

(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 439 393 A2

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
21.07.2004 Bulletin 2004/30

(51) Int Cl.7: **G01N 33/574, G01N 33/53**(21) Application number: **03257868.4**(22) Date of filing: **15.12.2003**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IT LI LU MC NL PT RO SE SI SK TR**
Designated Extension States:
AL LT LV MK

(30) Priority: **13.12.2002 US 433554 P**
31.07.2003 US 491397 P

(71) Applicants:
• **Bayer Healthcare LLC**
Tarrytown, New York 10591-5097 (US)
• **MAYO FOUNDATION FOR MEDICAL**
EDUCATION AND RESEARCH
Rochester, MN 55905 (US)

(72) Inventors:
• **Astle, Jon H.**
Taunton, MA 02780 (US)
• **Boardman, Lisa Allyn**
Rochester, MN 55902 (US)
• **Bugart, Lawrence J.**
Rochester, MN 55901 (US)
• **Burgess, Christopher C.**
Westwood, MA 02090 (US)
• **Catino, Theodore J.**
Attleboro, MA 02702 (US)

- **Dwivedi, Poornima**
Alamo, CA 94507 (US)
- **Huntress, Maryanne**
Attleboro, MA 02703 (US)
- **Johnson, Karen Anne**
Action, MA 01720 (US)
- **Lewis, Marcia E.**
Cohasset, MA 02025 (US)
- **Maimonis, Peter J.**
Westwood, MA 02090 (US)
- **Myerow, Susan H.**
Lexington, MA 02421 (US)
- **Brown-Shimer, Sheryl Lynn Andrea**
Boston, MA 02118 (US)
- **Thiagalingam, Arunthathi**
Lexington, MA 02420 (US)
- **Thibodeau, Stephen N.**
Rochester, MN 55906 (US)
- **Molino, Gary A.**
Norfolk, MA 02056 (US)

(74) Representative: **Grant, Anne Rosemary**
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL (GB)

(54) **Detection methods using TIMP 1 for colon cancer diagnosis**

(57) The present invention relates to a method for detecting the presence of colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 α or TIMP1 nucleic acid or amino acid molecules in a clinical sample obtained from the patient, wherein Reg1 α or TIMP1 expression is indicative of the presence of colorectal cancer. The invention further relates to a method for detecting the presence of

colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 α or TIMP1 nucleic acid or amino acid molecules in a clinical sample, in addition to detecting the presence of one or more additional colorectal cancer associated markers.

EP 1 439 393 A2

Description

5 [0001] Colorectal carcinoma is a malignant neoplastic disease. There is a high incidence of colorectal carcinoma in the Western world, particularly in the United States. Tumors of this type often metastasize through lymphatic and vascular channels. Many patients with colorectal carcinoma eventually die from this disease. In fact, it is estimated that 62,000 persons in the United States alone die of colorectal carcinoma annually.

10 [0002] However, if diagnosed early, colorectal cancer may be treated effectively by surgical removal of the cancerous tissue. Colorectal cancers originate in the colorectal epithelium and typically are not extensively vascularized (and therefore not invasive) during the early stages of development. Colorectal cancer is thought to result from the clonal expansion of a single mutant cell in the epithelial lining of the colon or rectum. The transition to a highly vascularized, invasive and ultimately metastatic cancer which spreads throughout the body commonly takes ten years or longer. If the cancer is detected prior to invasion, surgical removal of the cancerous tissue is an effective cure. However, colorectal cancer is often detected only upon manifestation of clinical symptoms, such as pain and black tarry stool. Generally, such symptoms are present only when the disease is well established, often after metastasis has occurred, and the prognosis for the patient is poor, even after surgical resection of the cancerous tissue. Early detection of colorectal cancer therefore is important in that detection may significantly reduce its morbidity.

15 [0003] Invasive diagnostic methods such as endoscopic examination allow for direct visual identification, removal, and biopsy of potentially cancerous growths such as polyps. Endoscopy is expensive, uncomfortable, inherently risky, and therefore not a practical tool for screening populations to identify those with colorectal cancer. Non-invasive analysis of stool samples for characteristics indicative of the presence of colorectal cancer or precancer is a preferred alternative for early diagnosis, but no known diagnostic method is available which reliably achieves this goal. A reliable, non-invasive, and accurate technique for diagnosing colorectal cancer at an early stage would help save many lives.

20 [0004] Ectopic expression of the pancreatic regenerating gene (RegI) has been identified previously in colorectal tumors, and suggested as a potential marker for colorectal cancer (Zenilman et al., (1997) *J. Gastrointest. Surg.*, 1: 194; Watanabe et al., (1990) *J. Biol. Chem.*, 265: 7432; Birse and Rosen, WO01/12781). At present, there is no reliable method known to those of skill in the art for the rapid and accurate detection of Reg1 α in the serum of colorectal cancer patients (Satomura et al., (1995) *J. Gastroenterol.* 30: 643). There is thus a need in the art for a method of detecting, and/or monitoring colorectal cancer in a patient utilizing the expression of Reg1 α in serum.

25 [0005] The present invention provides a method of detecting, monitoring or determining the therapeutic response of colorectal cancer in an individual as well as compositions, and kits for performing the method. In its most general aspect, the method comprises: obtaining a clinical sample from the individual and detecting the presence of one or more of the nucleic acid sequences of SEQ ID Nos. 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos. 2, 4, or 72-138.

30 [0006] The invention also provides a method of detecting, monitoring or determining the therapeutic response of colorectal cancer in an individual as well as compositions, and kits for performing the method, which, in its preferred aspect, comprises: obtaining a clinical sample from the individual and detecting the presence of Reg1 α or TIMP1 in said sample, wherein the presence of Reg1 α or TIMP1 in the sample is indicative of the presence or stage of colorectal cancer in the individual.

35 [0007] In one embodiment, the step of detecting comprises: contacting said clinical sample with a ligand which is capable of binding to Reg1 α or TIMP1 under conditions which permit the ligand to bind to Reg1 α or TIMP1; and detecting the binding of the ligand to Reg1 α or TIMP1, wherein detection of binding is indicative of the presence of Reg1 α or TIMP1 in the sample. The polypeptide ligand may comprise, for example, an antibody, peptide, oligonucleotide, or other molecule that specifically binds Reg1 α or TIMP1. In a currently preferred embodiment, the clinical sample comprises serum.

40 [0008] The present invention further provides a method of detecting, monitoring, or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from said individual; and detecting the presence of Reg1 α or TIMP1 and at least one other colorectal cancer associated marker in the sample, wherein the presence of Reg1 α or TIMP1 and the at least one other colorectal cancer associated marker is indicative of colorectal cancer in the individual. The colorectal cancer associated marker may comprise, for example, one or more of the nucleic acid sequences of SEQ ID Nos 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos 2, 4, or 72-138, or derivatives or homologs thereof having substantially the same binding specificity.

45 [0009] In a preferred embodiment, the above step of detecting comprises contacting a serum sample with a first ligand which is capable of binding to Reg1 α or TIMP1 and a second ligand which is capable of binding to the colorectal cancer associated marker, under conditions which permit the first and second ligands to bind to Reg1 α or TIMP1 and the colorectal cancer associated marker, respectively; and detecting the binding of the first ligand to Reg1 α or TIMP1 and the second ligand to the colorectal cancer associated marker, wherein detection of binding is indicative of the presence of Reg1 α or TIMP1 and the colorectal cancer associated marker in said sample. The polypeptide ligand may comprise, for example, an antibody, peptide, oligonucleotide, or other molecule that specifically binds

Reg1 α or TIMP1.

[0010] The present invention also provides a method of detecting, monitoring or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from an individual; and detecting the presence of a nucleic acid molecule which encodes Reg1 α or TIMP 1 in said sample, wherein the presence of the nucleic acid molecule in the sample is indicative of colorectal cancer in the individual.

[0011] The invention still further provides a method of detecting, monitoring or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from an individual; and detecting the presence of a nucleic acid molecule which encodes Reg1 α or TIMP1 and at least one other nucleic acid molecule which encodes at least one other colorectal cancer associated marker in the sample, wherein the presence of the nucleic acid sequence encoding Reg1 α or TIMP1 and the nucleic acid sequence encoding the at least one other colorectal cancer associated marker is indicative of colorectal cancer in the individual. In a preferred embodiment, the colorectal cancer associated marker is one or more of the nucleic acid sequences of SEQ ID Nos 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos 2, 4, or 72-138, or derivatives or homologs thereof having substantially the same binding specificity.

[0012] Figure 1 shows the level of Reg1 α polypeptide present in serum obtained from normal control patients (n=35), patients diagnosed with inflammatory bowel disease (IBD; n=7), patients diagnosed with cirrhosis (n=7), and patients diagnosed with colorectal cancer (n=63).

[0013] Figure 2 shows the level of Reg1 α polypeptide measured in the colorectal cancer patient group (n=63) differentiated based on cancer severity. The degree of cancer has been established by Dukes'-type staging, and data from patients with Dukes'-type A, B, C, and D is shown.

[0014] Figure 3 shows a graphical representation of the plasma level of TIMP 1 polypeptides, along with one or more other colorectal cancer associated markers obtained from patients with colorectal cancer.

[0015] The present invention is based, in part, on the discovery that the expression of the human islet regenerating protein, Reg1 α , is increased in patients with colorectal cancer, and as such is a valuable marker for the identification of colorectal cancer in humans. The present invention further provides for the early detection of colorectal cancer by detecting the presence of Reg1 α or TIMP1 (and optionally, one or more additional colorectal cancer associated markers) in a clinical sample from an individual. The invention provides further, the ability to monitor the recurrence of colorectal cancer in a patient wherein colorectal cancer has been previously detected, by monitoring the levels of Reg1 α or TIMP1 polypeptide or polynucleotide sequences present in a clinical sample from the patient, wherein an increase in Reg1 α or TIMP1 in the sample is indicative of the recurrence of colorectal cancer. The invention provides still further, the ability to monitor the decrease in colorectal cancer in response to a therapeutic agent, whereby the levels of Reg1 α or TIMP1 are measured in a clinical sample obtained from a patient who has received therapeutic treatment for colorectal cancer, wherein a decrease in the levels of Reg1 α or TIMP1 detected in the clinical sample from the patient is indicative of the efficacy of the therapeutic treatment. In any of the preceding embodiments, Reg1 α or TIMP1 polynucleotide or polypeptide expression levels are measured in concert with at least one additional colorectal cancer associated marker.

[0016] Accordingly, the present invention relates in part to novel methods for identifying cancer in an individual, particularly colorectal cancer, by screening for genes or gene products, which are over or underexpressed in cancer relative to the level of expression in normal tissue, such as colon tissue. Alternatively, the invention provides a method for the identification of cancer in an individual by screening for genes or gene products which are over- or underexpressed in colorectal cancer, and which are detectable in a clinical sample of an individual with colorectal cancer.

[0017] In a preferred embodiment, the present invention relates to methods useful for the detection of colorectal cancer in an individual, preferably a human patient by detecting serum levels of Reg1 α or TIMP1. The invention relates to methods for colorectal cancer detection that utilize either or both techniques of detecting the presence of the Reg1 α or TIMP1 gene or detecting the Reg1 α or TIMP1 encoded polypeptide product in the serum of an individual, or alternatively in a clinical sample from an individual.

[0018] The present invention further provides methods for the identification of colorectal cancer wherein cancer is detected by the identification of Reg1 α or TIMP1 expression in a patient clinical sample, in combination with the expression in the same sample of at least one other colorectal cancer associated marker. This combination of Reg1 α or TIMP1 detection analysis, in concert with the detection of additional colon-cancer markers provides an efficient and reliable method for detecting the presence of colorectal cancer.

[0019] The methods described herein which specifically refer to the detection of Reg1 α , may equally be applied to the detection of TIMP1 by one of skill in the art, based on the disclosure of the present specification:

[0020] As used herein, "Reg1 α " refers to a polypeptide molecule having the sequence of either of SEQ ID Nos 2 or 4. Reg1 α as used herein, also refers to a polypeptide which is encoded by either of the sequences of SEQ ID Nos. 1 or 3. The sequences of SEQ ID Nos 2 and 4 each represent a functional Reg1 α protein, but differ from each other by four amino acids in the leader sequence which is cleaved off during protein synthesis.

[0021] As used herein, "TIMP 1" refers to a polypeptide molecule having the sequence of SEQ ID NO: 100. TIMP1 as used herein, also refers to a nucleotide which is encoded by the sequence of SEQ ID NO: 33, or a functional homolog

thereof.

[0022] As used herein, a "clinical sample" refers to a tissue, cellular, or fluid sample obtained from an individual. A "clinical sample", as used herein, can refer to a cells, circulating cells (e.g., circulating cells in blood), cells obtained from specific anatomical locations, or specific cell types (e.g., colon cell, gastrointestinal cell, cancerous cell, etc.), a tissue sample, or physiological fluids such as lymph, bile, serum, plasma, urine, synovial fluid, blood, CSF, mucus membrane secretions, or other physiological samples such as stool. Preferably, the clinical sample is serum or plasma. A colorectal cancer associated marker of the invention, such as TIMP1, may be detected in a suitable "clinical sample" where the suitability of a particular type of clinical sample for the detection of a specific colorectal cancer associated marker may be readily determined by one of skill in the art.

[0023] As used herein, "detecting" refers to the identification of the presence or absence of a molecule in a sample. Where the molecule to be detected is a polypeptide, the step of detecting can be performed by binding the polypeptide with an antibody that is detectably labeled. A detectable label is a molecule which is capable of generating, either independently, or in response to a stimulus, an observable signal. A detectable label can be, but is not limited to a fluorescent label, a chromogenic label, a luminescent label, or a radioactive label. Methods for "detecting" a label include quantitative and qualitative methods adapted for standard or confocal microscopy, FACS analysis, and those adapted for high throughput methods involving multiwell plates, arrays or microarrays. One of skill in the art can select appropriate filter sets and excitation energy sources for the detection of fluorescent emission from a given fluorescent polypeptide or dye. "Detecting" as used herein can also include the use of multiple antibodies to a polypeptide to be detected, wherein the multiple antibodies bind to different epitopes on the polypeptide to be detected. Antibodies used in this manner can employ two or more detectable labels, and can include, for example a FRET pair. A polypeptide molecule, such as Reg1 α , is "detected" according to the present invention when the level of detectable signal is at all greater than the background level of the detectable label, or where the level of measured nucleic acid is at all greater than the level measured in a control sample.

[0024] As used herein, "detecting" as it refers to detecting the presence of a target nucleic acid molecule (e.g., a nucleic acid molecule encoding Reg1 α , or other colorectal cancer-specific sequence) refers to a process wherein the signal generated by a directly or indirectly labeled probe nucleic acid molecule (capable of hybridizing to a target, e.g., a sequence encoding Reg1 α , in a serum sample) is measured or observed. Thus, detection of the probe nucleic acid is directly indicative of the presence, and thus the detection, of a target nucleic acid, such as a sequence encoding Reg1 α . For example, if the detectable label is a fluorescent label, the target nucleic acid (e.g., the nucleic acid molecule encoding Reg1 α) is "detected" by observing or measuring the light emitted by the fluorescent label on the probe nucleic acid when it is excited by the appropriate wavelength, or if the detectable label is a fluorescence/quencher pair, the target nucleic acid is "detected" by observing or measuring the light emitted upon association or dissociation of the fluorescence/quencher pair present on the probe nucleic acid, wherein detection of the probe nucleic acid indicates detection of the target nucleic acid. If the detectable label is a radioactive label, the target nucleic acid, following hybridization with a radioactively labeled probe is "detected" by, for example, autoradiography. Methods and techniques for "detecting" fluorescent, radioactive, and other chemical labels may be found in Ausubel et al. (1995, Short Protocols in Molecular Biology, 3rd Ed. John Wiley and Sons, Inc.). Alternatively, a nucleic acid may be "indirectly detected" wherein a moiety is attached to a probe nucleic acid which will hybridize with the target, such as an enzyme activity, allowing detection in the presence of an appropriate substrate, or a specific antigen or other marker allowing detection by addition of an antibody or other specific indicator. Alternatively, a target nucleic acid molecule can be detected by amplifying a nucleic acid sample prepared from a patient clinical sample, using oligonucleotide primers which are specifically designed to hybridize with a portion of the target nucleic acid sequence. Quantative amplification methods, such as, but not limited to TaqMan, may also be used to "detect" a target nucleic acid according to the invention. A nucleic acid molecule is "detected" as used herein where the level of nucleic acid measured (such as by quantitative PCR), or the level of detectable signal provided by the detectable label is at all above the background level.

[0025] As used herein, "detecting" refers further to the early detection of colorectal cancer in a patient, wherein "early" detection refers to the detection of colorectal cancer at Dukes stage A or preferably, prior to a time when the colorectal cancer is morphologically able to be classified in a particular Dukes stage. "Detecting" as used herein further refers to the detection of colorectal cancer recurrence in an individual, using the same detection criteria as indicated above. "Detecting" as used herein still further refers to the measuring of a change in the degree of colorectal cancer before and/or after treatment with a therapeutic agent. In this case, a change in the degree of colorectal cancer in response to a therapeutic agent refers to an increase or decrease in the expression of Reg1 α (and optionally, one or more additional colorectal cancer associated markers), or alternatively, in the amount of Reg1 α polypeptide (and optionally, one or more additional colorectal cancer associated markers) present in a clinical sample by at least 10% in response to the presence of a therapeutic agent relative to the expression level in the absence of the therapeutic agent.

[0026] As used herein, "individual" refers to a mammal, preferably a human.

[0027] As used herein, a "ligand" refers to a molecule which is capable of binding a polypeptide. A "polypeptide ligand" useful in the present invention includes, but is not limited to an antibody, a monoclonal antibody, a polyclonal

antibody, an antibody fragment (e.g., Fv, scFv, or Fab), a small molecule, or a nucleic acid aptamer. A "ligand" as used herein can also refer to a "nucleic acid ligand", such as an oligonucleotide, polynucleotide, DNA, RNA, mRNA, or cDNA, which is capable of binding to a complementary nucleic acid molecule, or polypeptide molecule.

[0028] The term "antibody" as used herein is intended to include whole antibodies, e.g., of any isotype (IgG, IgA, IgM, IgE, etc), and includes fragments thereof, and single-chain antibodies, which also are specifically reactive with a vertebrate, e.g., mammalian, protein. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. Thus, the term includes segments of proteolytically-cleaved or recombinantly-prepared portions of an antibody molecule that are capable of selectively reacting with a certain protein. Nonlimiting examples of such proteolytic and/or recombinant fragments include Fab, F (ab')₂, Fab', Fv, and single chain antibodies (scFv) containing a V[L] and/or V[H] domain joined by a peptide linker. The scFv's may be covalently or non-covalently linked to form antibodies having two or more binding sites. The subject invention includes polyclonal, monoclonal, or other purified preparations of antibodies and recombinant antibodies.

[0029] As used herein, a "colorectal cancer associated marker" refers to a polypeptide or nucleic acid sequence which exhibits over- or underexpression of at least 10% in colorectal cancer cells, tissue, or serum obtained from an individual having colorectal cancer, relative to the level of expression in cells, tissue, or serum obtained from an individual that does not have colorectal cancer. Non-limiting examples of colorectal cancer associated markers useful in the present invention include the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, and/or the polypeptide molecules of SEQ ID Nos 2, 4, 72-138. In one embodiment, the polypeptide sequences of SEQ ID Nos 2, 4, 72-138 are encoded by the nucleic acid sequences of 1, 3, 5-71, respectively. A "colorectal cancer specific marker" useful in the invention may be a polypeptide or nucleic acid sequence which exhibits over- or underexpression in colorectal cancer as described above, but which may also be over or underexpressed in other, non-colorectal types of cancer. Alternatively, a "colorectal cancer associated marker", as used herein, may refer to a carbohydrate epitope present on a polypeptide or nucleic acid molecule and/or an antibody molecule which recognizes and is capable of binding to such an epitope, wherein the carbohydrate epitope is known to be associated with the presence of colorectal cancer in an individual. Such carbohydrate epitopes may be present on more than one unrelated protein or polypeptide. In one embodiment, such a carbohydrate epitope is CA 19-9, also known as sialyl-Lewis^a, is a tumor marker defined by a monoclonal antibody as a carbohydrate epitope, related to the blood group antigens, composed of a branching, 5-sugar structure covalently bound to a variety of glycoproteins or glycolipids. The proteins primarily belong to the mucin family and the lipids are usually membrane associated. The CA 19-9 epitope is typically the terminal moiety of a complex, O-linked carbohydrate structure on either macromolecule. Other tumor markers also defined as various carbohydrate epitopes useful in the present invention as a "colorectal cancer associated marker" include CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and the Du-PAN's 1 -5.

[0030] The term "interact" as used herein is meant to include detectable interactions (e.g., biochemical interactions) between molecules, such as interaction between protein-protein, protein-nucleic acid, nucleic acid-nucleic acid, and protein-small molecule or nucleic acid-small molecule in nature.

[0031] As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded polynucleotides. ESTs, chromosomes, cDNAs, mRNAs, and rRNAs are representative examples of molecules that may be referred to as nucleic acids.

[0032] The terms "protein", "polypeptide", and "peptide" are used interchangeably herein when referring to a gene product. As used herein, "polypeptide" refers to any kind of polypeptide such as peptides, human proteins, fragments of human proteins, proteins or fragments of proteins from non-human sources, engineered versions proteins or fragments of proteins, enzymes, antigens, drugs, molecules involved in cell signaling, such as receptor molecules, antibodies, including polypeptides of the immunoglobulin superfamily, such as antibody polypeptides or T-cell receptor polypeptides.

[0033] As used herein, the term "level of expression" refers to the measurable expression level of a given nucleic acid. The level of expression of a nucleic acid is determined by methods well known in the art. The "level of expression" may measured by hybridization analysis using labeled target nucleic acids according to methods well known in the art (see, for example, Ausubel et al., Short Protocols in Molecular Biology, 3rd Ed. 1995, John Wiley and Sons, Inc.). The label on the target nucleic acid is a luminescent label, an enzymatic label, a radioactive label, a chemical label or a physical label. Preferably, the target nucleic acids are labeled with a fluorescent molecule. Preferred fluorescent labels include fluorescein, amino coumarin acetic acid, tetramethylrhodamine isothiocyanate (TRITC), Texas Red, Cy3 and Cy5. Alternatively, the "level of expression" can be measured by quantitative amplification protocols, such as TaqMan, known to those of skill in the art.

[0034] The term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of preferred vector is an episome, i. e., a nucleic acid capable of extra-chromosomal replication. Preferred vectors are those capable of autonomous replication and/or expression of nucleic acids to which they

are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer generally to circular double stranded DNA loops which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

Reg1 α and TIMP1 nucleic acid

[0035] As described above, the present invention relates to the detection of Reg1 α or TIMP1 polypeptide in a clinical sample from an individual, preferably a serum or plasma sample, thus permitting the detection of colorectal cancer. The present invention, however, equally relates to the identification of the nucleic acid sequence which encodes Reg1 α or TIMP1 as a marker for colorectal cancer.

[0036] Nucleic acid and amino acid sequences of Reg1 α are shown in SEQ ID Nos 1 or 3, and 2 or 4, respectively. Nucleic acid and amino acid sequences of TIMP1 are shown in SEQ ID NO: 33 and 100 respectively. While the invention relates to the direct detection of either of the sequences of Reg1 α or TIMP1 in a method for detecting colorectal cancer, the invention further relates to the detection of sequences complementary thereto, or a sequence which specifically hybridizes to a sequence of SEQ ID Nos. 1, 3, or 33. The present invention also relates to the detection of colorectal cancer by detecting the presence, in a clinical sample, of a nucleic acid molecule which encodes the sequence of SEQ ID Nos. 2, 4, or 100, or a fragment thereof.

[0037] Another aspect of the invention provides the detection of colorectal cancer by the detection of a nucleic acid which hybridizes under low, medium, or high stringency conditions to a nucleic acid sequence represented by one or more of SEQ ID Nos. 1, 3, or 33, or a sequence complementary thereto. Appropriate stringency conditions which promote DNA hybridization, for example, 6.0 x sodium chloride/sodium citrate (SSC) at about 45 °C, followed by a wash of 2.0 x SSC at 50°C, are known to those skilled in the art or can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-12.3.6. For example, the salt concentration in the wash step can be selected from a low stringency of about 2.0 x SSC at 50°C to a high stringency of about 0.2 x SSC at 50°C. In addition, the temperature in the wash step can be increased from low stringency conditions at room temperature, about 22 °C, to high stringency conditions at about 65 °C. Both temperature and salt may be varied, or temperature or salt concentration may be held constant while the other variable is changed. In a preferred embodiment, a nucleic acid encoding Reg1 α or TIMP1 will bind to SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or a fragment thereof, under moderately stringent conditions, for example at about 2.0 x SSC and about 40°C. In a particularly preferred embodiment, a Reg1 α or TIMP1 nucleic acid sequence present in a patient clinical sample will bind of SEQ ID Nos. 1, 3, or 33, respectively, or a sequence complementary thereto, or fragment thereof, under high stringency conditions.

[0038] In one embodiment, the invention provides nucleic acids which hybridize under low stringency conditions of 6 x SSC at room temperature followed by a wash at 2 x SSC at room temperature.

[0039] In another embodiment, the invention provides nucleic acids which hybridize under high stringency conditions of 2 x SSC at about 65 °C followed by a wash at 0.2 x SSC at about 65 °C.

[0040] Detection of Reg1 α nucleic acids having a sequence that differs from the nucleotide sequences shown in SEQ ID Nos. 1 or 3, or a sequence complementary thereto, due to degeneracy in the genetic code, are also within the scope of the invention. Such nucleic acids encode functionally equivalent peptides (i.e., a peptide having equivalent or similar biological activity) but differ in sequence from the sequence shown in the sequence listing due to degeneracy in the genetic code. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC each encode histidine) may result in "silent" mutations which do not affect the amino acid sequence of a polypeptide. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the subject polypeptides will exist among mammals. One skilled in the art will appreciate that these variations in one or more nucleotides (e.g., up to about 3-5% of the nucleotides) of the nucleic acids encoding polypeptides having an activity of a polypeptide may exist among individuals of a given species due to natural allelic variation.

[0041] The invention also includes within its scope a polynucleotide which hybridizes under stringent conditions (at least about 4 x SSC at 65 °C, or at least about 4 x SSC at 42 °C; see, for example, U.S. Patent No. 5,707,829, incorporated herein by reference) with at least 15 contiguous nucleotides of SEQ ID Nos. 1 or 3. By this is intended that when at least 15 contiguous nucleotides of SEQ ID Nos. 1 or 3 is used as a probe, the probe will preferentially hybridize with a gene or mRNA (of the biological material) comprising the complementary sequence, allowing the identification and retrieval of the nucleic acids (i.e., Reg1 α) of the biological material that uniquely hybridize to the selected probe. Probes of more than 15 nucleotides can be used, but 15 nucleotides represents enough sequence for unique identification.

[0042] Constructs of polynucleotides having the sequence of SEQ ID Nos. 1 or 3, a portion thereof, or a sequence

complementary thereto, and useful, for example for generating a probe, can be produced synthetically, or obtained from natural sources (e.g., human cells) using methods well known to those of skill in the art (see, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989).

5

Calculation of Sequence Homology

[0043] In one embodiment, the present invention relates to the detection of colorectal cancer in an individual by detecting the presence of Reg1 α or TIMP1 or a sequence homologous thereto, by using probes and/or primers which are complementary to portions of the Reg1 α or TIMP1 sequence, or are sufficiently homologous to portions of the Reg1 α or TIMP1 sequence to permit hybridization of the probes and/or primers to Reg1 α or TIMP1 under high stringency conditions. Sequences of the invention are at least 50% homologous to Reg1 α or TIMP1, and are preferably 60%, 70%, 80%, 90% homologous up to complete sequence identity with Reg1 α or TIMP1 (or optionally to a sequence encoding one or more additional colorectal cancer associated markers).

[0044] Sequence identity with respect to any of the sequences presented herein can be determined by a simple "eyeball" comparison (i.e. a strict comparison) of any one or more of the sequences with another sequence to see if that other sequence has, for example, at least 80% sequence identity to the sequence(s).

[0045] Relative sequence identity can also be determined by commercially available computer programs that can calculate % identity between two or more sequences using any suitable algorithm for determining identity, using for example default parameters. A typical example of such a computer program is CLUSTAL. Other computer program methods to determine identity and similarity between two sequences include but are not limited to the GCG program package (Devereux *et al* 1984 *Nucleic Acids Research* 12: 387) and FASTA (Atschul *et al* 1990 *J Molec Biol* 403-410).

[0046] % homology may be calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in one sequence is directly compared with the corresponding amino acid in the other sequence, one residue at a time. This is called an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of residues.

[0047] Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause the following amino acid residues to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence comparison methods are designed to produce optimal alignments that take into consideration possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting "gaps" in the sequence alignment to try to maximise local homology.

[0048] However, these more complex methods assign "gap penalties" to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared sequences - will achieve a higher score than one with many gaps. "Affine gap costs" are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimized alignments with fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is preferred to use the default values when using such software for sequence comparisons. For example, when using the GCG Wisconsin Bestfit package the default gap penalty for amino acid sequences is -12 for a gap and -4 for each extension.

[0049] Calculation of maximum % homology therefore firstly requires the production of an optimal alignment, taking into consideration gap penalties. A suitable computer program for carrying out such an alignment is the GCG Wisconsin Bestfit package (University of Wisconsin, U.S.A.; Devereux *et al.*, 1984, *Nucleic Acids Research* 12:387). Examples of other software that can perform sequence comparisons include, but are not limited to, the BLAST package (Ausubel *et al.*, 1995, *Short Protocols in Molecular Biology*, 3rd Edition, John Wiley & Sons), FASTA (Atschul *et al.*, 1990, *J. Mol. Biol.*, 403-410) and the GENWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (Ausubel *et al.*, 1999 *supra*, pages 7-58 to 7-60).

[0050] Although the final % homology can be measured in terms of identity, the alignment process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled similarity score matrix is generally used that assigns scores to each pairwise comparison based on chemical similarity or evolutionary distance. An example of such a matrix commonly used is the BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin programs generally use either the public default values or a custom symbol comparison table if supplied. It is preferred to use the public default values for the GCG package, or in the case of other software, the default matrix, such as BLOSUM62.

[0051] Advantageously, the BLAST algorithm is employed, with parameters set to default values. The BLAST algorithm is described in detail on the World Wide Web at ncbi.nih.gov/BLAST/blast_help.html, which is incorporated herein by reference. The search parameters are defined as follows, and can be advantageously set to the defined default

parameters.

[0052] Advantageously, "substantial identity" when assessed by BLAST equates to sequences which match with an EXPECT value of at least about 7, preferably at least about 9 and most preferably 10 or more. The default threshold for EXPECT in BLAST searching is usually 10.

5 [0053] BLAST (Basic Local Alignment Search Tool) is the heuristic search algorithm employed by the programs blastp, blastn, blastx, tblastn, and tblastx; these programs ascribe significance to their findings using the statistical methods of Karlin and Altschul (Karlin and Altschul 1990, *Proc. Natl. Acad. Sci. USA* 87:2264-68; Karlin and Altschul, 1993, *Proc. Natl. Acad. Sci. USA* 90:5873-7; see http://www.ncbi.nih.gov/BLAST/blast_help.html) with a few enhancements. The BLAST programs are tailored for sequence similarity searching, for example to identify homologues to a query sequence. For a discussion of basic issues in similarity searching of sequence databases, see Altschul *et al*

10 (1994) *Nature Genetics* 6:119-129.

[0054] The five BLAST programs available on the World Wide Web at ncbi.nlm.nih.gov perform the following tasks: **blastp** - compares an amino acid query sequence against a protein sequence database; **blastn** - compares a nucleotide query sequence against a nucleotide sequence database; **blastx** - compares the six-frame conceptual translation products of a nucleotide query sequence (both strands) against a protein sequence database; **tblastn** - compares a protein query sequence against a nucleotide sequence database dynamically translated in all six reading frames (both strands); **tblastx** - compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database.

[0055] BLAST uses the following search parameters:

20 [0056] HISTOGRAM - Display a histogram of scores for each search; default is yes. (See parameter H in the BLAST Manual).

[0057] DESCRIPTIONS - Restricts the number of short descriptions of matching sequences reported to the number specified; default limit is 100 descriptions. (See parameter V in the manual page).

25 [0058] EXPECT - The statistical significance threshold for reporting matches against database sequences; the default value is 10, such that 10 matches are expected to be found merely by chance, according to the stochastic model of Karlin and Altschul (1990). If the statistical significance ascribed to a match is greater than the EXPECT threshold, the match will not be reported. Lower EXPECT thresholds are more stringent, leading to fewer chance matches being reported. Fractional values are acceptable. (See parameter E in the BLAST Manual).

30 [0059] CUTOFF - Cutoff score for reporting high-scoring segment pairs. The default value is calculated from the EXPECT value (see above). HSPs are reported for a database sequence only if the statistical significance ascribed to them is at least as high as would be ascribed to a lone HSP having a score equal to the CUTOFF value. Higher CUTOFF values are more stringent, leading to fewer chance matches being reported. (See parameter S in the BLAST Manual). Typically, significance thresholds can be more intuitively managed using EXPECT.

35 [0060] ALIGNMENTS - Restricts database sequences to the number specified for which high-scoring segment pairs (HSPs) are reported; the default limit is 50. If more database sequences than this happen to satisfy the statistical significance threshold for reporting (see EXPECT and CUTOFF below), only the matches ascribed the greatest statistical significance are reported. (See parameter B in the BLAST Manual).

40 [0061] MATRIX - Specify an alternate scoring matrix for BLASTP, BLASTX, TBLASTN and TBLASTX. The default matrix is BLOSUM62 (Henikoff & Henikoff, 1992). The valid alternative choices include: PAM40, PAM120, PAM250 and IDENTITY. No alternate scoring matrices are available for BLASTN; specifying the MATRIX directive in BLASTN requests returns an error response.

[0062] STRAND - Restrict a TBLASTN search to just the top or bottom strand of the database sequences; or restrict a BLASTN, BLASTX or TBLASTX search to just reading frames on the top or bottom strand of the query sequence.

45 [0063] FILTER - Mask off segments of the query sequence that have low compositional complexity, as determined by the SEG program of Wootton & Federhen (1993) *Computers and Chemistry* 17:149-163, or segments consisting of short-periodicity internal repeats, as determined by the XNU program of Claverie & States (1993) *Computers and Chemistry* 17:191-201, or, for BLASTN, by the DUST program of Tatusov and Lipman (see <http://www.ncbi.nlm.nih.gov>). Filtering can eliminate statistically significant but biologically uninteresting reports from the blast output (e.g., hits against common acidic-, basic- or proline-rich regions), leaving the more biologically interesting regions of the query sequence available for specific matching against database sequences.

50 [0064] Low complexity sequence found by a filter program is substituted using the letter "N" in nucleotide sequence (e.g., "NNNNNNNNNNNNNN") and the letter "X" in protein sequences (e.g., "XXXXXXXXXX").

[0065] Filtering is only applied to the query sequence (or its translation products), not to database sequences. Default filtering is DUST for BLASTN, SEG for other programs.

55 [0066] It is not unusual for nothing at all to be masked by SEG, XNU, or both, when applied to sequences in SWISS-PROT, so filtering should not be expected to always yield an effect. Furthermore, in some cases, sequences are masked in their entirety, indicating that the statistical significance of any matches reported against the unfiltered query sequence should be suspect.

[0067] NCBI-gi - Causes NCBI gi identifiers to be shown in the output, in addition to the accession and/or locus name.
 [0068] Most preferably, sequence comparisons are conducted using the simple BLAST search algorithm provided on the World Wide Web at ncbi.nlm.nih.gov/BLAST. In some embodiments of the present invention, no gap penalties are used when determining sequence identity.

5

Probes and Primers

[0069] The nucleotide sequence of Reg1 α or TIMP1 is useful in the present invention for the generation of probes and primers designed for identifying the Reg1 α or TIMP1 nucleic acid sequence in a patient sample such as serum, colon cells or tissue. Nucleotide sequences useful as probes/primers may include all or a portion of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or sequences which hybridize under stringent conditions to all or a portion of SEQ ID No. 1, 3 or 33. For instance, the present invention also provides a probe/primer comprising a substantially purified oligonucleotide, which oligonucleotide comprising a nucleotide sequence that hybridizes under stringent conditions to at least approximately 8, preferably about 12, preferably about 15, preferably about 25, more preferably about 40 consecutive nucleotides up to the full length of the sense or anti-sense sequence of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or a naturally occurring mutant thereof. For instance, primers based on the nucleic acid represented in SEQ ID No. 1, 3 or 33, or a sequence complementary thereto, can be used in a reaction to amplify a template nucleic acid (e.g., Reg1 α) contained within an mRNA sample derived from a patient clinical sample.

[0070] Not only are probes based on the nucleic acid sequence encoding Reg1 α or TIMP1 useful for detecting Reg1 α or TIMP1, but they can also provide a method for detecting mutations in wild-type Reg1 α or TIMP1 in a patient. Nucleic acid probes which are complementary to a wild-type Reg1 α or TIMP1 and can form mismatches with mutant genes are provided, allowing for detection by enzymatic or chemical cleavage or by shifts in electrophoretic mobility. Likewise, probes based on the subject sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins, for use, for example, in prognostic or diagnostic assays. In preferred embodiments, the nucleic acid probe further comprises a label group attached thereto and able to be detected, e.g., the label group is selected from a radioisotope, a fluorescent compound, a chemiluminescent compound, a chromagenic compound, an enzyme, and enzyme co-factor.

[0071] Full-length cDNA molecules comprising the disclosed nucleic acids, useful for the generation of probes, primers, or for transcription to produce the Reg1 α or TIMP1 protein itself, or antibodies thereto may be obtained as follows. The nucleic acid sequence of Reg1 α or TIMP1 or a portion thereof comprising at least approximately 8, preferably about 12, preferably about 15, preferably about 25, more preferably about 40 nucleotides up to the full length of the sequence of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, may be used as a hybridization probe to detect hybridizing members of a cDNA library using probe design methods, cloning methods, and clone selection techniques as described in U.S. Patent No. 5,654,173, "Secreted Proteins and Polynucleotides Encoding Them," incorporated herein by reference. Libraries of cDNA may be made from selected tissues, such as normal or tumor tissue, or from tissues of a mammal treated with, for example, a pharmaceutical agent. Preferably, the tissue is the same as that used to generate the nucleic acids, as both the nucleic acid and the cDNA represent expressed genes. Alternatively, many cDNA libraries are available commercially. (Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989). The choice of cell type for library construction may be made after the identity of the protein encoded by the nucleic acid-related gene is known. This will indicate which tissue and cell types are likely to express the related gene, thereby containing the mRNA for generating the cDNA.

[0072] Members of the library that are larger than the nucleic acid, and preferably that contain the whole sequence of the native message, may be obtained. To confirm that the entire cDNA has been obtained, RNA protection experiments may be performed as follows. Hybridization of a full-length cDNA to an mRNA may protect the RNA from RNase degradation. If the cDNA is not full length, then the portions of the mRNA that are not hybridized may be subject to RNase degradation. This may be assayed, as is known in the art, by changes in electrophoretic mobility on polyacrylamide gels, or by detection of released mononucleotides. Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989). In order to obtain additional sequences 5' to the end of a partial cDNA, 5' RACE (PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc. 1990)) may be performed.

[0073] Genomic DNA (e.g., Reg1 α genomic DNA) may be isolated using nucleic acids in a manner similar to the isolation of full-length cDNAs. Briefly, the nucleic acids, or portions thereof, may be used as probes to libraries of genomic DNA. Preferably, the library is obtained from the cell type that was used to generate the nucleic acids. Most preferably, the genomic DNA is obtained from the biological material described herein in the Example. Such libraries may be in vectors suitable for carrying large segments of a genome, such as P1 or YAC, as described in detail in Sambrook et al., pages 9.4-9.30. In addition, genomic sequences can be isolated from human BAC libraries, which are commercially available from Research Genetics, Inc., Huntsville, Alabama, USA, for example. In order to obtain addi-

tional 5' or 3' sequences, chromosome walking may be performed, as described in Sambrook et al., such that adjacent and overlapping fragments of genomic DNA are isolated. These may be mapped and pieced together, as is known in the art, using restriction digestion enzymes and DNA ligase.

[0074] Using the nucleic acids of the invention, corresponding full length genes can be isolated using both classical and PCR methods to construct and probe cDNA libraries. Using either method, Northern blots, preferably, may be performed on a number of cell types to determine which cell lines express the gene of interest at the highest rate.

[0075] Classical methods of constructing cDNA libraries in Sambrook et al., supra. With these methods, cDNA can be produced from mRNA and inserted into viral or expression vectors. Typically, libraries of mRNA comprising poly(A) tails can be produced with poly(T) primers. Similarly, cDNA libraries can be produced using the instant Reg1 α sequence or portions thereof as primers.

[0076] PCR methods may be used to amplify the members of a cDNA library that comprise the desired insert. In this case, the desired insert may contain sequence from the full length cDNA that corresponds to the sequence encoding Reg1 α . Such PCR methods include gene trapping and RACE methods.

[0077] Gene trapping may entail inserting a member of a cDNA library into a vector. The vector then may be denatured to produce single stranded molecules. Next, a substrate-bound probe, such as a biotinylated oligo, may be used to trap cDNA inserts of interest. Biotinylated probes can be linked to an avidin-bound solid substrate. PCR methods can be used to amplify the trapped cDNA. To trap sequences corresponding to the full length genes, the labeled probe sequence may be based on the nucleic acid of SEQ ID Nos. 1 or 3, or a sequence complementary thereto. Random primers or primers specific to the library vector can be used to amplify the trapped cDNA. Such gene trapping techniques are described in Gruber et al., PCT WO 95/04745 and Gruber et al., U.S. Pat. No. 5,500,356. Kits are commercially available to perform gene trapping experiments from, for example, Life Technologies, Gaithersburg, Maryland, USA.

[0078] "Rapid amplification of cDNA ends," or RACE, is a PCR method of amplifying cDNAs from a number of different RNAs. The cDNAs may be ligated to an oligonucleotide linker and amplified by PCR using two primers. One primer may be based on sequence from the instant nucleic acids, for which full length sequence is desired, and a second primer may comprise a sequence that hybridizes to the oligonucleotide linker to amplify the cDNA. A description of this method is reported in PCT Pub. No. WO 97/19110.

[0079] In preferred embodiments of RACE, a common primer may be designed to anneal to an arbitrary adaptor sequence ligated to cDNA ends (Apte and Siebert, *Biotechniques* 15:890-893, 1993; Edwards et al., *Nuc. Acids Res.* 19:5227-5232, 1991). When a single gene-specific RACE primer is paired with the common primer, preferential amplification of sequences between the single gene specific primer and the common primer occurs. Commercial cDNA pools modified for use in RACE are available.

[0080] Once the full-length cDNA or gene is obtained, DNA encoding variants can be prepared by site-directed mutagenesis, described in detail in Sambrook 15.3-15.63. The choice of codon or nucleotide to be replaced can be based on the disclosure herein on optional changes in amino acids to achieve altered protein structure and/or function.

[0081] As an alternative method to obtaining DNA or RNA from a biological material, such as serum, nucleic acid comprising nucleotides having the sequence of one or more nucleic acids of the invention can be synthesized. Thus, the invention encompasses nucleic acid molecules ranging in length from about 8 nucleotides (corresponding to at least 12 contiguous nucleotides which hybridize under stringent conditions to or are at least 80% identical to the nucleic acid sequence of SEQ ID Nos. 1 or 3, or a sequence complementary thereto) up to a maximum length suitable for one or more biological manipulations, including replication and expression, of the nucleic acid molecule. The invention includes but is not limited to (a) nucleic acid having the size of the full Reg1 α gene, or a sequence complementary thereto; (b) the nucleic acid of (a) also comprising at least one additional gene, operably linked to permit expression of a fusion protein; (c) an expression vector comprising (a) or (b); (d) a plasmid comprising (a) or (b); and (e) a recombinant viral particle comprising (a) or (b).

[0082] The sequence of a nucleic acid of the present invention is not limited and can be any sequence of A, T, G, and/or C (for DNA) and A, U, G, and/or C (for RNA) or modified bases thereof, including inosine and pseudouridine. The choice of sequence will depend on the desired function and can be dictated by coding regions desired, the intron-like regions desired, and the regulatory regions desired.

Probe preparation

[0083] Prior to hybridization of a probe nucleic acid to a patient sample, the nucleic acid samples must be prepared to facilitate subsequent detection of hybridization. The nucleic acid samples obtained from an individual (including nucleic acid sequences encoding Reg1 α , and optionally, at least one other colorectal cancer associated marker) to be screened for colorectal cancer are capable of being bound by a nucleic acid probe of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation.

[0084] Probes useful in the invention for hybridizing to and thus identifying the presence of Reg1 α or TIMP1, and

optionally, at least one additional colorectal cancer associated marker may be designed to hybridize to a polynucleotide molecule derived from an mRNA transcript coding for Reg1 α , or optionally, at least one additional colorectal cancer associated marker. As used herein, a "polynucleotide derived from an mRNA transcript" refers to a polynucleotide for which synthesis of the mRNA transcript or a subsequence thereof has ultimately served as a template. Thus, a cDNA reverse transcribed from an mRNA, an RNA transcribed from that cDNA, a DNA amplified from the cDNA, an RNA transcribed from the amplified DNA, etc., are all derived from the mRNA transcript and detection of such derived products is indicative of the presence and/or abundance of the original transcript in a sample. Thus, suitable target nucleic acid samples include, but are not limited to, mRNA transcripts of a gene or genes (i.e., Reg1 α or a colorectal cancer associated marker), cDNA reverse transcribed from the mRNA, cRNA transcribed from the cDNA, DNA amplified from a gene or genes, RNA transcribed from amplified DNA, and the like. The polynucleotide probes used herein are preferably designed to hybridize to Reg1 α , or optionally to a sequence encoding at least one other colorectal cancer associated marker.

[0085] Nucleic acid probes may be generated using techniques which are well known to those of skill in the art (see, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989), or *Current Protocols in Molecular Biology*, F. Ausubel et al., ed. Greene Publishing and Wiley-Interscience, New York (1987).

[0086] In order to measure the hybridization of a probe nucleic acid to a target sequence in a sample, the probe nucleic acid is preferably labeled with a detectable label. Any analytically detectable marker that is attached to or incorporated into a molecule may be used in the invention. An analytically detectable marker refers to any molecule, moiety or atom which is analytically detected and quantified.

[0087] Detectable labels suitable for use in the present invention include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads (e.g., DynabeadsTM), fluorescent dyes (e.g., fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (e.g., ³H, ¹²⁵I, ³⁵S, ¹⁴C, or ³²P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241.

[0088] Means of detecting such labels are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film or scintillation counters, fluorescent markers may be detected using a photodetector to detect emitted light. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate, and colorimetric labels are detected by simply visualizing the colored label.

[0089] The labels may be incorporated into a nucleic acid probe by any of a number of means well known to those of skill in the art. However, in a preferred embodiment, the label is simultaneously incorporated into the probe during an amplification step in the preparation of the probe polynucleotides. Thus, for example, polymerase chain reaction (PCR), or other amplification reaction, with labeled primers or labeled nucleotides will provide a labeled amplification product, and thus a labeled probe.

[0090] Alternatively, a label may be added directly to the probe. Means of attaching labels to polynucleotides are well known to those of skill in the art and include, for example nick translation or end-labeling (e.g. with a labeled RNA) and subsequent attachment (ligation) of a polynucleotide linker joining the sample polynucleotide to a label (e.g., a fluorophore).

[0091] In a preferred embodiment, the fluorescent modifications are by cyanine dyes e.g. Cy-3/Cy-5 dUTP, Cy-3/Cy-5 dCTP (Amersham Pharmacia) or alexa dyes (Khan, J., Simon, R., Bittner, M., Chen, Y., Leighton, S. B., Pohida, T., Smith, P. D., Jiang, Y., Gooden, G. C., Trent, J. M. & Meltzer, P. S. (1998) *Cancer Res.* 58, 50095013.).

[0092] In a preferred embodiment, a probe nucleic acid which is capable of hybridizing to Reg 1 α and a probe nucleic acid which is capable of hybridizing to a nucleic acid sequence encoding at least one additional colorectal cancer associated marker, are co-hybridized to a test sample (e.g., a serum sample). In this embodiment, the two probe samples used for comparison are labeled with different fluorescent dyes which produce distinguishable detection signals, for example, probes hybridizable with Reg 1 α are labeled with Cy5 and probes hybridizable with another colorectal cancer associated marker are labeled with Cy3. The differently labeled target samples are hybridized to the same microarray simultaneously.

[0093] In a preferred embodiment, a control probe may be co-hybridized to a sample along with a probe for Reg1 α and/or a probe for an additional colorectal cancer associated marker, wherein the control probe is capable of hybridizing to a nucleic acid sequence known to be found in the clinical sample, for example, where the clinical sample is a serum sample, a control sequence may be a sequence encoding serum albumin, or fibrinogen.

Vectors and Host Cells

[0094] The present invention further provides vectors and plasmids useful for directing the expression of Reg1 α or TIMP1 or other colorectal cancer associated markers, and further provides host cells which express the vectors and plasmids provided herein. Nucleic acid sequences useful for the expression from a vector or plasmid as described below include, but are not limited to any nucleic acid or gene sequence identified as being differentially regulated by the methods described above, and further include therapeutic nucleic acid molecules, such as antisense molecules. The host cell may be any prokaryotic or eukaryotic cell. Ligating the polynucleotide sequence into a gene construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures well known in the art.

Vectors

[0095] There is a wide array of vectors known and available in the art that are useful for the expression of differentially expressed nucleic acid molecules according to the invention. The selection of a particular vector clearly depends upon the intended use the polypeptide encoded by the differentially expressed nucleic acid. For example, the selected vector must be capable of driving expression of the polypeptide in the desired cell type, whether that cell type be prokaryotic or eukaryotic. Many vectors comprise sequences allowing both prokaryotic vector replication and eukaryotic expression of operably linked gene sequences.

[0096] Vectors useful according to the invention may be autonomously replicating, that is, the vector, for example, a plasmid, exists extrachromosomally and its replication is not necessarily directly linked to the replication of the host cell's genome. Alternatively, the replication of the vector may be linked to the replication of the host's chromosomal DNA, for example, the vector may be integrated into the chromosome of the host cell as achieved by retroviral vectors.

[0097] Vectors useful according to the invention preferably comprise sequences operably linked to the sequence of interest (e.g., Reg1 α) that permit the transcription and translation of the sequence. Sequences that permit the transcription of the linked sequence of interest include a promoter and optionally also include an enhancer element or elements permitting the strong expression of the linked sequences. The term "transcriptional regulatory sequences" refers to the combination of a promoter and any additional sequences conferring desired expression characteristics (e.g., high level expression, inducible expression, tissue- or cell-type-specific expression) on an operably linked nucleic acid sequence.

[0098] The selected promoter may be any DNA sequence that exhibits transcriptional activity in the selected host cell, and may be derived from a gene normally expressed in the host cell or from a gene normally expressed in other cells or organisms. Examples of promoters include, but are not limited to the following: A) prokaryotic promoters - *E. coli* lac, tac, or trp promoters, lambda phage P_R or P_L promoters, bacteriophage T7, T3, Sp6 promoters, *B. subtilis* alkaline protease promoter, and the *B. stearothermophilus* maltogenic amylase promoter, etc.; B) eukaryotic promoters - yeast promoters, such as GAL1, GAL4 and other glycolytic gene promoters (see for example, Hitzeman et al., 1980, J. Biol. Chem. 255: 12073-12080; Alber & Kawasaki, 1982, J. Mol. Appl. Gen. 1: 419-434), LEU2 promoter (Martinez-Garcia et al., 1989, Mol Gen Genet. 217: 464-470), alcohol dehydrogenase gene promoters (Young et al., 1982, in Genetic Engineering of Microorganisms for Chemicals, Hollaender et al., eds., Plenum Press, NY), or the TP11 promoter (U.S. Pat. No. 4,599,311); insect promoters, such as the polyhedrin promoter (U.S. Pat. No. 4,745,051; Vasuvedan et al., 1992, FEBS Lett. 311: 7-11), the P10 promoter (Vlak et al., 1988, J. Gen. Virol. 69: 765-776), the *Autographa californica* polyhedrosis virus basic protein promoter (EP 397485), the baculovirus immediate-early gene promoter gene 1 promoter (U.S. Pat. Nos. 5,155,037 and 5,162,222), the baculovirus 39K delayed-early gene promoter (also U.S. Pat. Nos. 5,155,037 and 5,162,222) and the OpMNPV immediate early promoter 2; mammalian promoters - the SV40 promoter (Subramani et al., 1981, Mol. Cell. Biol. 1: 854-864), metallothionein promoter (MT-1; Palmiter et al., 1983, Science 222: 809-814), adenovirus 2 major late promoter (Yu et al., 1984, Nucl. Acids Res. 12: 9309-21), cytomegalovirus (CMV) or other viral promoter (Tong et al., 1998, Anticancer Res. 18: 719-725), or even the endogenous promoter of a gene of interest in a particular cell type.

[0099] A selected promoter may also be linked to sequences rendering it inducible or tissue-specific. For example, the addition of a tissue-specific enhancer element upstream of a selected promoter may render the promoter more active in a given tissue or cell type. Alternatively, or in addition, inducible expression may be achieved by linking the promoter to any of a number of sequence elements permitting induction by, for example, thermal changes (temperature sensitive), chemical treatment (for example, metal ion- or IPTG-inducible), or the addition of an antibiotic inducing agent (for example, tetracycline).

[0100] Regulatable expression is achieved using, for example, expression systems that are drug inducible (e.g., tetracycline, rapamycin or hormone-inducible). Drug-regulatable promoters that are particularly well suited for use in mammalian cells include the tetracycline regulatable promoters, and glucocorticoid steroid-, sex hormone steroid-, ecdysone-, lipopolysaccharide (LPS)- and isopropylthiogalactoside (IPTG)-regulatable promoters. A regulatable ex-

pression system for use in mammalian cells should ideally, but not necessarily, involve a transcriptional regulator that binds (or fails to bind) nonmammalian DNA motifs in response to a regulatory agent, and a regulatory sequence that is responsive only to this transcriptional regulator.

[0101] Tissue-specific promoters may also be used to advantage in differentially expressed sequence-encoding constructs of the invention. A wide variety of tissue-specific promoters is known. As used herein, the term "tissue-specific" means that a given promoter is transcriptionally active (i.e., directs the expression of linked sequences sufficient to permit detection of the polypeptide product of the promoter) in less than all cells or tissues of an organism. A tissue specific promoter is preferably active in only one cell type, but may, for example, be active in a particular class or lineage of cell types (e.g., hematopoietic cells). A tissue specific promoter useful according to the invention comprises those sequences necessary and sufficient for the expression of an operably linked nucleic acid sequence in a manner or pattern that is essentially the same as the manner or pattern of expression of the gene linked to that promoter in nature. The following is a non-exclusive list of tissue specific promoters and literature references containing the necessary sequences to achieve expression characteristic of those promoters in their respective tissues; the entire content of each of these literature references is incorporated herein by reference. Examples of tissue specific promoters useful in the present invention are as follows:

[0102] Bowman et al., 1995 Proc. Natl. Acad. Sci. USA 92, 12115-12119 describe a brain-specific transferrin promoter; the synapsin I promoter is neuron specific (Schoch et al., 1996 J. Biol. Chem. 271, 3317-3323); the nestin promoter is post-mitotic neuron specific (Uetsuki et al., 1996 J. Biol. Chem. 271, 918-924); the neurofilament light promoter is neuron specific (Charron et al., 1995 J. Biol. Chem. 270, 30604-30610); the acetylcholine receptor promoter is neuron specific (Wood et al., 1995 J. Biol. Chem. 270, 30933-30940); and the potassium channel promoter is high-frequency firing neuron specific (Gan et al., 1996 J. Biol. Chem. 271, 5859-5865). Any tissue specific transcriptional regulatory sequence known in the art may be used to advantage with a vector encoding a differentially expressed nucleic acid sequence obtained from an animal subjected to pain.

[0103] In addition to promoter/enhancer elements, vectors useful according to the invention may further comprise a suitable terminator. Such terminators include, for example, the human growth hormone terminator (Palmiter et al., 1983, supra), or, for yeast or fungal hosts, the TPI1 (Alber & Kawasaki, 1982, supra) or ADH3 terminator (McKnight et al., 1985, EMBO J. 4: 2093-2099).

[0104] Vectors useful according to the invention may also comprise polyadenylation sequences (e.g., the SV40 or Ad5E1b poly(A) sequence), and translational enhancer sequences (e.g., those from Adenovirus VA RNAs). Further, a vector useful according to the invention may encode a signal sequence directing the recombinant polypeptide to a particular cellular compartment or, alternatively, may encode a signal directing secretion of the recombinant polypeptide.

a. Plasmid vectors.

[0105] Any plasmid vector that allows expression of a coding sequence of interest (e.g., the coding sequence of Reg1 α) in a selected host cell type is acceptable for use according to the invention. A plasmid vector useful in the invention may have any or all of the above-noted characteristics of vectors useful according to the invention. Plasmid vectors useful according to the invention include, but are not limited to the following examples: Bacterial - pQE70, pQE60, pQE-9 (Qiagen) pBs, phagescript, psiX174, pBluescript SK, pBsKS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia); Eukaryotic - pWLneo, pSV2cat, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other plasmid or vector may be used as long as it is replicable and viable in the host.

b. Bacteriophage vectors.

[0106] There are a number of well known bacteriophage-derived vectors useful according to the invention. Foremost among these are the lambda-based vectors, such as Lambda Zap II or Lambda-Zap Express vectors (Stratagene) that allow inducible expression of the polypeptide encoded by the insert. Others include filamentous bacteriophage such as the M13-based family of vectors.

c. Viral vectors.

[0107] A number of different viral vectors are useful according to the invention, and any viral vector that permits the introduction and expression of one or more of the polynucleotides of the invention in cells is acceptable for use in the methods of the invention. Viral vectors that can be used to deliver foreign nucleic acid into cells include but are not limited to retroviral vectors, adenoviral vectors, adeno-associated viral vectors, herpesviral vectors, and Semliki forest viral (alphaviral) vectors. Defective retroviruses are well characterized for use in gene transfer (for a review see Miller,

A.D. (1990) *Blood* 76:271). Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F.M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14, and other standard laboratory manuals.

[0108] In addition to retroviral vectors, Adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle (see for example Berkner et al., 1988, *BioTechniques* 6:616; Rosenfeld et al., 1991, *Science* 252:431-434; and Rosenfeld et al., 1992, *Cell* 68:143-155). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 dl324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are well known to those skilled in the art. Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al., 1992, *Curr. Topics in Micro. and Immunol.* 158:97-129). An AAV vector such as that described in Traschin et al. (1985, *Mol. Cell. Biol.* 5:3251-3260) can be used to introduce nucleic acid into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors. (see, for example, Hermonat et al., 1984, *Proc. Natl. Acad. Sci. USA* 81: 6466-6470; and Traschin et al., 1985, *Mol. Cell. Biol.* 4: 2072-2081).

Host cells

[0109] Any cell into which a recombinant vector carrying a gene of interest (e.g., a sequence encoding Reg1 α) may be introduced and wherein the vector is permitted to drive the expression of the peptide encoded by the differentially expressed sequence is useful according to the invention. Any cell in which a differentially expressed molecule of the invention may be expressed and preferably detected is a suitable host, wherein the host cell is preferably a mammalian cell and more preferably a human cell. Vectors suitable for the introduction of nucleic acid sequences to host cells from a variety of different organisms, both prokaryotic and eukaryotic, are described herein above or known to those skilled in the art.

[0110] Host cells may be prokaryotic, such as any of a number of bacterial strains, or may be eukaryotic, such as yeast or other fungal cells, insect or amphibian cells, or mammalian cells including, for example, rodent, simian or human cells. Cells may be primary cultured cells, for example, primary human fibroblasts or keratinocytes, or may be an established cell line, such as NIH3T3, 293T or CHO cells. Further, mammalian cells useful in the present invention may be phenotypically normal or oncogenically transformed. It is assumed that one skilled in the art can readily establish and maintain a chosen host cell type in culture.

Introduction of vectors to host cells.

[0111] Vectors useful in the present invention may be introduced to selected host cells by any of a number of suitable methods known to those skilled in the art. For example, vector constructs may be introduced to appropriate bacterial cells by infection, in the case of *E. coli* bacteriophage vector particles such as lambda or M 13, or by any of a number of transformation methods for plasmid vectors or for bacteriophage DNA. For example, standard calcium-chloride-mediated bacterial transformation is still commonly used to introduce naked DNA to bacteria (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY), but electroporation may also be used (Ausubel et al., 1988, Current Protocols in Molecular Biology, (John Wiley & Sons, Inc., NY, NY)).

[0112] For the introduction of vector constructs to yeast or other fungal cells, chemical transformation methods are generally used (e.g. as described by Rose et al., 1990, Methods in Yeast Genetics, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY). For transformation of *S. cerevisiae*, for example, the cells are treated with lithium acetate to achieve transformation efficiencies of approximately 10⁴ colony-forming units (transformed cells)/ μ g of DNA. Transformed cells are then isolated on selective media appropriate to the selectable marker used. Alternatively, or in addition, plates or filters lifted from plates may be scanned for GFP fluorescence to identify transformed clones.

[0113] For the introduction of vectors comprising a sequence of interest to mammalian cells, the method used will depend upon the form of the vector. Plasmid vectors may be introduced by any of a number of transfection methods, including, for example, lipid-mediated transfection ("lipofection"), DEAE-dextran-mediated transfection, electroporation or calcium phosphate precipitation. These methods are detailed, for example, in Current Protocols in Molecular Biology (Ausubel et al., 1988, John Wiley & Sons, Inc., NY, NY).

[0114] Lipofection reagents and methods suitable for transient transfection of a wide variety of transformed and non-transformed or primary cells are widely available, making lipofection an attractive method of introducing constructs to eukaryotic, and particularly mammalian cells in culture. For example, LipofectAMINE™ (Life Technologies) or LipoTaxi™ (Stratagene) kits are available. Other companies offering reagents and methods for lipofection include Bio-Rad Laboratories, CLONTECH, Glen Research, In Vitrogen, JBL Scientific, MBI Fermentas, PanVera, Promega, Quantum Biotechnologies, Sigma-Aldrich, and Wako Chemicals USA.

[0115] Following transfection with a vector of the invention, eukaryotic (e.g., human) cells successfully incorporating the construct (intra- or extrachromosomally) may be selected, as noted above, by either treatment of the transfected population with a selection agent, such as an antibiotic whose resistance gene is encoded by the vector, or by direct screening using, for example, FACS of the cell population or fluorescence scanning of adherent cultures. Frequently, both types of screening may be used, wherein a negative selection is used to enrich for cells taking up the construct and FACS or fluorescence scanning is used to further enrich for cells expressing differentially expressed polynucleotides or to identify specific clones of cells, respectively. For example, a negative selection with the neomycin analog G418 (Life Technologies, Inc.) may be used to identify cells that have received the vector, and fluorescence scanning may be used to identify those cells or clones of cells that express the vector construct to the greatest extent.

Reg1 α and TIMP1 Polypeptides

[0116] The present invention provides a method for the detection of colorectal cancer in an individual by detecting the presence of Reg1 α or TIMP1 in a clinical sample from an individual. In addition the invention encompasses the detection of cancer by identifying Reg1 α or TIMP1 gene product in colon tissue or cells. Alternatively, the invention relates to a method for the detection of colorectal cancer in an individual wherein colorectal cancer is identified by detecting the presence of Reg1 α or TIMP1 and at least one additional colorectal cancer associated marker in the clinical sample from an individual. Polypeptides of the present invention, the detection of which is indicative of colorectal cancer include those having the sequence shown in one or more of SEQ ID Nos. 2, 4, or 100, or alternatively, which are encoded by one or more of SEQ ID Nos. 1, 3 or 33.

[0117] Preferred polypeptides which can be detected and are thus indicative of colorectal cancer in an individual are those that are encoded by nucleic acid sequences at least about 70%, 75%, 80%, 90%, 95%, 97%, or 98% identical to a mRNA sequence complementary to the nucleic acid sequence of SEQ ID Nos. 1, 3 or 33. Particularly preferred polypeptides are those of SEQ ID Nos. 2, 4, or 99, or fragments thereof, or polypeptide sequences which are at least about 70%, 75%, 80%, 90%, 95%, 98% or 99% identical in sequence to the amino acid sequence of one or more of SEQ ID Nos. 2, 4, or 100.

[0118] In addition to a method for detecting colorectal cancer by identifying the presence of the Reg1 α or TIMP1 polypeptide in a clinical sample from an individual, the invention further comprises a method of detecting cancer by identifying the presence of Reg1 α or TIMP1 in addition to at least one other colorectal cancer associated marker in the same sample (e.g., in the same serum, tissue, or cell sample).

Antibodies

[0119] The invention provides a method for colorectal cancer detection comprising the step of detecting the presence of Reg1 α or TIMP1 (and optionally, at least one additional colorectal cancer associated marker) in a clinical sample from an individual. In one embodiment, the presence of Reg1 α or TIMP1, or other marker, in such a sample is detected using a polypeptide ligand which is preferably detectably labeled, and is capable of binding to Reg1 α or TIMP1, and if present, the other marker, in the sample. In a preferred embodiment, the polypeptide ligand is an antibody. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized, or chimeric antibodies, single chain antibodies, Fab fragments, Fv fragments F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic antibodies, or other epitope binding polypeptide. Preferably, an antibody, useful in the present invention for the detection of Reg1 α or TIMP1 (and optionally at least one additional colorectal cancer associated marker), is a human antibody or fragment thereof, including scFv, Fab, Fab', F(ab'), Fd, single chain antibody, or Fv. Antibodies, useful in the invention may include a complete heavy or light chain constant region, or a portion thereof, or an absence thereof. An antibody, useful in the invention, may be obtained from an art recognized host, such as rabbit, mouse, rat, donkey, sheep, goat, guinea pig, camel, horse, or chicken. In one embodiment, an antibody, useful in the invention can be a humanized antibody, in which amino acids have been replaced in the non-antigen binding regions in order to more closely resemble a human antibody, while still retaining the original binding ability. Methods for making humanized antibodies are described in Teng et al., 1983, *Proc. Natl. Acad. Sci. USA* 80: 7308-7312; Kozbor et al., 1983, *Immunology Today* 4: 7279; Olsson et al., 1982, *Meth. Enzymol.* 92: 3-16; WO 92/06193; EP 0239400.

[0120] Antibodies of the present invention may be monospecific, dispecific, trispecific, or of greater multispecificity. As such, Reg1 α or TIMP1 and optionally an additional colorectal cancer associated marker useful for the detection of colorectal cancer may be detected with separate antibodies, or may be detected with the same antibody. Alternatively, a multispecific antibody may exhibit different specificities for different epitopes on the same protein (e.g., different epitopes on Reg1 α). While specificity of an antibody useful in the present invention to either Reg1 α or one or more additional colorectal cancer associated markers is preferred, antibodies that bind polypeptides with at least 95%, 90%, 85%, 75%, 65%, 55%, and at least 50% identity to a polypeptide useful in the present invention for the detection of

colorectal cancer (i.e., Reg1 α , and/or an additional colorectal cancer associated marker) are also included in the present invention. Also encompassed in the present invention are antibodies which bind to polypeptide molecules which are encoded by one or more nucleic acid sequences which are complementary to, or hybridize to the sequences of SEQ ID Nos. 1, 3 or 33, or one or more sequences which are complementary to, or hybridize to a nucleic acid sequence which encodes an additional colorectal cancer associated marker as described herein.

[0121] Antibodies of the present invention which are useful for the detection of colorectal cancer may further act as agonists or antagonists of the activity of the polypeptide molecules to which they bind, and may thus be useful as therapeutic molecules for the treatment or prevention of colorectal cancer.

[0122] An important, but not limiting, role of an antibody of the present invention is to provide for the purification, or detection of Reg 1 α or TIMP1 or other colorectal cancer associated markers in a patient sample, including both in vitro and in vivo detection methods. Antibodies useful for the detection of colorectal cancer as described herein do not have to be used alone, and can be fused to other polypeptides, including a heterologous polypeptide at the N- or C-terminus of the antibody polypeptide sequence. For example, an antibody useful in the present invention may be fused with a detectable label to facilitate detection of the antibody when bound to a target polypeptide. Methods for detectably labeling an antibody polypeptide are known to those of skill in the art.

[0123] For the production of antibodies useful in the present invention, various hosts including goats, rabbits, rats, mice, etc., may be immunized by injection with the protein products (or any portion, fragment, or oligonucleotide thereof which retains immunogenic properties) of the candidate genes of the invention. Depending on the host species, various adjuvants may be used to increase the immunological response. Such adjuvants include but are not limited to Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol. BCG (bacilli Calmette-Guerin) and *Corynebacterium parvum* are potentially useful human adjuvants.

[0124] Polyclonal antisera or monoclonal antibodies can be made using methods known in the art. A mammal such as a mouse, hamster, or rabbit, can be immunized with an immunogenic form of a Reg1 α or TIMP1 polypeptide, fragment, modified form thereof, or variant form thereof. Alternatively, an animal may be immunized with an immunogenic form of one or more additional colorectal cancer associated marker polypeptides. Techniques for conferring immunogenicity on such molecules include conjugation to carriers or other techniques well known in the art. For example, the immunogenic molecule can be administered in the presence of adjuvant as described above. Immunization can be monitored by detection of antibody titers in plasma or serum. Standard immunoassay procedures can be used with the immunogen as antigen to assess the levels and the specificity of antibodies. Following immunization, antisera can be obtained and, if desired, polyclonal antibodies isolated from the sera.

[0125] To produce monoclonal antibodies, antibody producing cells (lymphocytes) can be harvested from an immunized animal and fused with myeloma cells by standard somatic cell fusion procedures thus immortalizing these cells and yielding hybridoma cells. Such techniques are well known in the art (see, e.g., Kohler and Milstein, 1975, *Nature* 256: 495-497; Kozbor et al., 1983, *Immunol. Today* 4: 72; Cole et al., 1985, In *Monoclonal Antibodies in Cancer Therapy*, Allen R. Bliss, Inc., pages 77-96). Additionally, techniques described for the production of single-chain antibodies (U. S. Patent No. 4,946,778) can be adapted to produce antibodies according to the invention.

[0126] Antibody fragments which can specifically bind to a polypeptide of the invention such as Reg1 α or TIMP1 or other colorectal cancer associated marker polypeptides, fragments thereof, modified forms thereof, and variants thereof, also may be generated by known techniques. For example, such fragments include, but are not limited to, F(ab')₂ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')₂ fragments. VH regions and FV regions can be expressed in bacteria using phage expression libraries (e.g., Ward et al., 1989, *Nature* 341: 544-546; Huse et al., 1989, *Science* 246: 1275-1281; McCafferty et al., 1990, *Nature* 348: 552-554).

[0127] Chimeric antibodies, i.e., antibody molecules that combine a non-human animal variable region and a human constant region also are within the scope of the invention. Chimeric antibody molecules include, for example, the antigen binding domain from an antibody of a mouse, rat, or other species, with human constant regions. Standard methods may be used to make chimeric antibodies containing the immunoglobulin variable region which recognizes the gene product of Reg1 α antigens of the invention (see, e.g., Morrison et al., 1985, *Proc. Natl. Acad. Sci. USA* 81: 6851; Takeda et al., 1985, *Nature* 314: 452; U.S. Patent No. 4,816,567; U.S. Patent No. 4,816,397).

Other Colorectal cancer Specific Analysis

[0128] In addition to the detection of colorectal cancer by identifying expression of Reg1 α or TIMP1, or detecting Reg1 α or TIMP1 polypeptides, the present invention further comprises a method for detecting colorectal cancer wherein a nucleic acid molecule encoding Reg1 α or TIMP1, or Reg 1 α or TIMP 1 polypeptide is identified in combination with at least one other nucleic acid sequence encoding a known colorectal cancer associated marker in a clinical sample from an individual. Alternatively, the presence of Reg1 α or TIMP1 is detected in combination with at least one additional

colorectal cancer marker amino acid sequence. Similar to the methods described above for Reg1 α , a nucleic acid molecule which encodes at least one other colorectal cancer associated marker may be used to generate a nucleic acid probe for detection of the colorectal cancer associated marker sequence in a patient sample, or may be used to generate amplification primers to amplify the colorectal cancer associated marker sequence from a patient sample comprising the sequence, thus identifying the presence of the colorectal cancer associated marker in the sample, and thus indicating the detection of colorectal cancer. A colorectal cancer associated marker polypeptide sequence may be used, as described above for Reg1 α to generate antibodies useful for detection of the colorectal cancer associated marker in a clinical sample. Methods for detecting a colorectal cancer associated marker nucleic acid or amino acid sequence are described below, and may be adapted from the methods for the detection of Reg1 α nucleic acid or amino acid in a clinical sample.

A "colorectal cancer associated marker" useful in the present invention, refers to a polypeptide or nucleic acid sequence which exhibits over- or underexpression of at least 10% in colorectal cancer cells, tissue, or serum obtained from an individual having colorectal cancer, relative to the level of expression in cells, tissue, or serum obtained from an individual that does not have colorectal cancer. Non-limiting examples of colorectal cancer associated markers useful in the present invention include the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, and/or the polypeptide molecules of SEQ ID Nos 2, 4, 72-138. In one embodiment, the polypeptide sequences of SEQ ID Nos 2, 4, 72-138 are encoded by the nucleic acid sequences of 1, 3, 5-71, respectively. It will be appreciated by one of skill in the art that, where the method of the invention relates to detection of Reg1 α and at least one other colorectal cancer associated marker, TIMP1 may be included as a potential "other colorectal cancer associated marker". Likewise, where the detection method is based on the detection of TIMP1 and at least one other colorectal cancer associated marker, Reg1 α may be included as a potential "other colorectal cancer associated marker". Alternatively, a colorectal cancer associated marker, as used in the present invention, may refer to a carbohydrate epitope present on a polypeptide or nucleic acid molecule and/or an antibody molecule which recognizes and is capable of binding to such an epitope, wherein the carbohydrate epitope is known to be associated with the presence of colorectal cancer in an individual. Such carbohydrate epitopes may be present on more than one unrelated protein or polypeptide. In one embodiment, such a carbohydrate epitope is CA 19-9, also known as sialyl-Lewis^a, is a tumor marker defined by a monoclonal antibody as a carbohydrate epitope, related to the blood group antigens, composed of a branching, 5-sugar structure covalently bound to a variety of glycoproteins or glycolipids. The proteins primarily belong to the mucin family and the lipids are usually membrane associated. The CA 19-9 epitope is typically the terminal moiety of a complex, O-linked carbohydrate structure on either macromolecule. Other tumor markers also defined as various carbohydrate epitopes useful in the present invention as a "colorectal cancer associated marker" include CA72-4 which is indicative of the presence of the Tag 72 antigen, which is a triply sialylated Tn antigen on varying protein backbones; Thomsen Freidenreich antigen (TF), which is a sialylated n-acetyl galactosamine moiety O-linked to various peptides; Tn and sialylated Tn (sTn) which is the backbone of the TF antigen without the terminal n-acetyl galactosamine moiety, O-linked to various peptides; CA 50 which is an epitope corresponding to sialylated Lewis A blood group antigen; CA 549 which is a CHO moiety on muc-1; CA 242 which is a sialylated CHO; LASA which is a lipid associated sialic acid, that is, a lipid without a protein associated to it; Du-PAN's 1-5, which are pancreatic associated mucin-like CHO antigens. These useful colon cancer specific antigens and others are known in the art and are described, for example, in "Serological Cancer Markers" Sell, S., Ed. 1992. Humana Press Inc., Totowa, NJ.

[0129] Table 1 below shows a list of "colorectal cancer associated markers" useful in the invention (although colorectal cancer associated markers useful in the invention are not limited to those shown in Table 1), and there correspondence with the sequences set forth in the "Sequence listing".

Table 1

SEQ ID NO	Gene Symbol	Length	Type	SEQ ID NO	Gene Symbol	Length	Type
5	CEACAM5	2974	DNA	72	CEACAM5	702	Protein
6	AFP	2032	DNA	73	AFP	609	Protein
7	IL8	1639	DNA	74	IL8	99	Protein
8	SPP1	1524	DNA	75	SPP1	300	Protein
9	KIAA1077	5500	DNA	76	KIAA1077	871	Protein
10	MMP12	1778	DNA	77	MMP12	470	Protein

11	UBD	777	DNA	78	UBD	165	Protein
12	COL1A1	5921	DNA	79	COL1A1	1464	Protein
13	LUM	1804	DNA	80	LUM	338	Protein
14	ENC1	4827	DNA	81	ENC1	589	Protein
15	PIGPC1	1098	DNA	82	PIGPC1	193	Protein
16	GTF3A	1381	DNA	83	GTF3A	423	Protein
17	CTSB	1978	DNA	84	CTSB	339	Protein
18	MCJ	1074	DNA	85	MCJ	150	Protein
19	SLC12A2	4098	DNA	86	SLC12A2	1212	Protein
20	C20orf42	3120	DNA	87	C20orf42	230	Protein
21	SDBCAG84	1337	DNA	88	SDBCAG84	383	Protein
22	NAP1L1	2908	DNA	89	NAP1L1	391	Protein
23	OSF-2	3213	DNA	90	OSF-2	836	Protein
24	COL6A3	10558	DNA	91	COL6A3	3176	Protein
25	SPARC	2133	DNA	92	SPARC	303	Protein
26	TGFBI	2691	DNA	93	TGFBI	683	Protein
27	FN1	8027	DNA	94	FN1	2355	Protein
28	COL1A2	5084	DNA	95	COL1A2	1366	Protein
29	S100A11	595	DNA	96	S100A11	105	Protein
30	LC27	2116	DNA	97	LC27	283	Protein
31	IRAK1	3583	DNA	98	IRAK1	712	Protein
32	IFITM2	905	DNA	99	IFITM2	132	Protein
33	TIMP1	782	DNA	100	TIMP1	207	Protein
34	IGFBP7	1124	DNA	101	IGFBP7	282	Protein
35	IFITM1	647	DNA	102	IFITM1	125	Protein
36	COL3A1	5489	DNA	103	COL3A1	1466	Protein

37	IGFBP5	1722	DNA	104	IGFBP5	272	Protein
38	RegIV	1200	DNA	105	RegIV	158	Protein
39	AGR2	1701	DNA	106	AGR2	175	Protein
40	HSPCA	2259	DNA	107	HSPCA	732	Protein
41	KIAA1199	7080	DNA	108	KIAA1199	1361	Protein
42	MMP1	1973	DNA	109	MMP1	469	Protein
43	MMP7	1127	DNA	110	MMP7	267	Protein
44	TSC	1163	DNA	111	TSC	216	Protein
45	HAIK1	2007	DNA	112	HAIK1	422	Protein
46	DAP3	1650	DNA	113	DAP3	398	Protein
47		2566	DNA	114		75	Protein
48		2067	DNA	115		163	Protein
49	KRT8	1752	DNA	116	KRT8	483	Protein
50	KRT18	1412	DNA	117	KRT18	430	Protein
51	KRT19	1407	DNA	118	KRT19	400	Protein
52	KRT20	1723	DNA	119	KRT20	424	Protein
53	MUC1	4139	DNA	120	MUC1	1255	Protein
54	MUC2	15720	DNA	121	MUC2	5179	Protein
55	MUC3	4707	DNA	122	MUC3	1217	Protein
56	MUC5AC	4151	DNA	123	MUC5AC	1373	Protein
57	CGB5	880	DNA	124	CGB5	165	Protein
58	EGFR	5532	DNA	125	EGFR	1210	Protein
59	ERBB2	4530	DNA	126	ERBB2	1255	Protein
60	FTH1	801	DNA	127	FTH1	190	Protein
61	FTL	878	DNA	128	FTL	175	Protein
62	ALPP	2747	DNA	129	ALPP	535	Protein

63	ODC1	2062	DNA	130	ODC1	461	Protein
64	MUC16	3557	DNA	131	MUC16	1148	Protein
65	CEACAM1	3464	DNA	132	CEACAM1	526	Protein
66	CEACAM3	1022	DNA	133	CEACAM3	212	Protein
67	CEACAM4	1190	DNA	134	CEACAM4	244	Protein
68	CEACAM6	2249	DNA	135	CEACAM6	344	Protein
69	CEACAM7	2292	DNA	136	CEACAM7	265	Protein
70	CEACAM8	2297	DNA	137	CEACAM8	349	Protein
71	CA9	1552	DNA	138	CA9	459	Protein

Detection Assays

[0130] The present invention provides method for detecting colorectal cancer, or alternatively, determining whether a subject is at risk for developing colorectal cancer by detecting the disclosed biomarkers (i.e., the nucleic acid sequence of Reg1 α or TIMP1 and optionally, one or more nucleic acid sequences encoding an additional colorectal cancer associated marker and/or polypeptide markers such as Reg1 α or TIMP1 and optionally, at least one additional colorectal cancer associated marker) for the disease or condition encoded thereby.

[0131] In clinical applications, human tissue samples, preferably serum, can be screened for the presence and/or absence of Reg1 α or TIMP1 and/or other colorectal cancer associated markers identified herein. Such samples may comprise tissue samples, whole cells, cell lysates, or isolated nucleic acids, including, for example, needle biopsy cores, surgical resection samples, lymph node tissue, or serum. A sample for analysis as described herein is preferably a serum sample. A serum sample may be obtained from an individual using methods which are well known to those of skill in the art. Briefly, a whole venous or arterial blood sample from an individual is collected into a test tube. The whole blood sample is permitted to incubate at room temperature for approximately 15-30 to allow the blood to clot. Once clotted, the sample is centrifuged at approximately 1500 to 3000 rpm for 5-30 minutes to completely separate the serum from the cellular components. This centrifugation may be repeated if necessary to achieve complete separation. The resulting serum sample may be subsequently screened for the presence of Reg1 α nucleic acid or amino acid and/or one or more additional colorectal cancer associated markers as described herein.

Screening for nucleic acid molecules

[0132] In one embodiment, the detection method of the present invention comprises determining whether a clinical sample from an individual contains mRNA of a colorectal cancer associated marker, preferably Reg1 α or TIMP1, but also optionally including additional colorectal cancer associated markers as described herein. Techniques for determining the presence of a nucleic acid molecule of interest include Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), in situ hybridization, PCR, and quantitative amplification.

[0133] Prior to detection of target nucleic acid molecules in a clinical sample, it is preferred to first isolate the mRNA from the sample to facilitate detection of the target sequence (i.e., a sequence encoding Reg1 α or TIMP1). Methods for isolation of mRNA from a biological sample are well known in the art. Briefly, where the sample is a serum sample, for example, 0.1 ml of 2 M sodium acetate, pH 4, 1 ml water-saturated phenol, and 0.2 ml of 49:1 chloroform/isoamyl alcohol are added to the serum sample sequentially. The sample is mixed after the addition of each component, and incubated for 15 min at 0-4°C after all components have been added. The sample is separated by centrifugation for 20 min at 10,000 x g, 4°C, precipitated by the addition of 1 ml of 100% isopropanol, incubated for 30 minutes at -20°C and pelleted by centrifugation for 10 minutes at 10,000 x g, 4°C. The resulting RNA pellet is dissolved in 0.3 ml denaturing solution, transferred to a microfuge tube, precipitated by the addition of 0.3 ml of 100% isopropanol for 30 minutes

at -20°C, and centrifuged for 10 minutes at 10,000 x g at 4°C. The RNA pellet is washed in 70% ethanol, dried, and resuspended in 100-200µl DEPC-treated water or DEPC-treated 0.5% SDS (Chomczynski and Sacchi, 1987, Anal. Biochem., 162: 156).

[0134] Alternatively, total RNA may be extracted from a clinical sample according to the present invention using a commercially available RNA isolation reagent such as Trizol (Invitrogen, Carlsbad, CA), following the manufacturers instructions. Purity and integrity of RNA is assessed by absorbance at 260/280 nm and separation of RNA samples on a 1% agarose gel followed by inspection under ultraviolet light.

[0135] Following mRNA isolation, the mRNA may be reverse transcribed to provide a cDNA sample according to methods well known to those of skill in the art (see, e.g., Ausubel et al. (1995), Short Protocols in Molecular Biology, 3rd Ed. John Wiley and Sons, Inc.)

[0136] Accordingly, in one aspect, the invention provides probes and primers that specifically hybridize to the Reg1α or TIMP1 nucleic acid sequences disclosed herein, or which can hybridize to a nucleic acid molecule encoding an additional colorectal cancer associated marker as described herein. Accordingly, the nucleic acid probes comprise a region of a nucleic acid sequence of SEQ ID Nos 1, 3, or 33 sufficient to hybridize with a nucleic acid substantially complementary to the sequence of SEQ ID Nos 1, 3 or 33. Preferred nucleic acid molecules for use as probes/primers can further comprise a region of nucleic acid sequence substantially complementary to the sequence of SEQ ID Nos. 1, 3 or 33 sufficient to hybridize with the sequence of SEQ ID Nos. 1, 3 or 33. In addition, nucleic acid sequences useful as probes/primers comprise a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably at least 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a marker nucleic acid sequence, which nucleic acid sequence is represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto.

[0137] In one embodiment, the method comprises using a nucleic acid probe to determine the presence of a Reg1α or TIMP1 nucleic acid molecule in a clinical sample (such as a serum sample or a nucleic acid sample extracted therefrom). Specifically, the method comprises:

1. Providing a nucleic acid probe comprising a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably at least about 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a nucleic acid sequence represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto;
2. Obtaining a clinical sample from a patient potentially comprising a Reg1α or TIMP1 nucleic acid sequence;
3. Providing a second clinical sample from an individual known to not have colorectal cancer;
4. Contacting the nucleic acid probe under stringent conditions with RNA of each of said first and second clinical samples (e.g., in a Northern blot or in situ hybridization assay); and
5. Comparing (a) the amount of hybridization of the probe with RNA of the first serum sample, with (b) the amount of hybridization of the probe with RNA of the second clinical sample; wherein a statistically significant difference in the amount of hybridization with the RNA of the first clinical sample as compared to the amount of hybridization with the RNA of the second clinical sample is indicative of the presence of Reg 1α or TIMP1 in the first clinical sample.

[0138] Although, primarily drawn to detection of Reg1α or TIMP1 in a clinical sample such as serum, in one aspect, the present invention provides a method comprising *in situ* hybridization detection of Reg1α or TIMP1 with a probe derived from a nucleic acid sequence represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto. Preferably, the hybridization probe is detectably labeled. The method comprises contacting the labeled hybridization probe with a tissue or cell sample from an individual suspected of having colorectal cancer, washing off any unbound probe, and detecting the signal produced by the detectable label, wherein the detection of the detectable signal is indicative of the presence of Reg1α or TIMP1 in the sample, and thus permits the detection of colorectal cancer. Alternatively, the tissue or cell is additionally hybridized with a detectably labeled nucleic acid probe which is capable of specifically hybridizing with a nucleic acid sequence that encodes at least one additional colorectal cancer associated marker. Detection of the second detectably labeled probe is thus indicative of the presence of the additional colorectal cancer associated marker in the sample, and in conjunction with the detection of Reg1α or TIMP1, permits the detection of colorectal cancer in the individual. Specific methods for *in situ* hybridization are well known in the art.

[0139] Alternatively, methods such as PCR, Northern analysis, and Taqman may be used to detect and/or quantitate

the expression of a nucleic acid sequence encoding Reg1 α in a clinical sample. In one embodiment, reverse transcription PCR (RT-PCR) is performed using primers designed to specifically hybridize to a predetermined portion of the Reg1 α mRNA sequence isolated from a clinical sample. Generation of a PCR product by such a reaction is thus indicative of the presence of the Reg1 α or TIMP1 sequence in the sample. The technique of designing primers for PCR amplification is well known in the art. Oligonucleotide primers and probes are 5 to 100 nucleotides in length, ideally from 17 to 40 nucleotides, although primers and probes of different length are of use. Primers for amplification are preferably about 17-25 nucleotides. Primers useful according to the invention are also designed to have a particular melting temperature (T_m) by the method of melting temperature estimation. Commercial programs, including Oligo™ (MBI, Cascade, CO), Primer Design and programs available on the internet, including Primer3 and Oligo Calculator can be used to calculate a T_m of a nucleic acid sequence useful according to the invention. Preferably, the T_m of an amplification primer useful according to the invention, as calculated for example by Oligo Calculator, is preferably between about 45 and 65° C and more preferably between about 50 and 60° C. Preferably, the T_m of a probe useful according to the invention is 7° C higher than the T_m of the corresponding amplification primers. It is preferred that, following generation of cDNA by RT-PCR, the cDNA fragment is cloned into an appropriate sequencing vector, such as a PCRII vector (TA cloning kit; Invitrogen). The identity of each cloned fragment is then confirmed by sequencing in both directions. It is expected that the sequence obtained from sequencing would be the same as the known sequence of Reg1 α to TIMP1 as described herein.

[0140] Alternatively, the presence of an mRNA sequence encoding Reg1 α or TIMP1 may be detected by Northern analysis. Sequence confirmed cDNAs, that is, cDNAs encoding Reg1 α or TIMP1 (or alternatively an additional colorectal cancer associated marker) are used to produce ³²P-labeled cDNA probes using techniques well known in the art (see, for example, Ausubel, *supra*). Labeled probes for Northern analysis may also be produced using commercially available kits (Prime-It Kit, Stratagene, La Jolla, CA). Northern analysis of total RNA obtained from a clinical sample may be performed using classically described techniques. For example, total RNA samples are denatured with formaldehyde / formamide and run for two hours in a 1 % agarose, MOPS-acetate-EDTA gel. RNA is then transferred to nitrocellulose membrane by upward capillary action and fixed by UV cross-linkage. Membranes are pre-hybridized for at least 90 minutes and hybridized overnight at 42° C. Post hybridization washes are performed as known in the art (Ausubel, *supra*). The membrane is then exposed to x-ray film overnight with an intensifying screen at -80° C. Labeled membranes are then visualized after exposure to film. The signal produced on the x-ray film by the radiolabeled cDNA probes can then be quantified using any technique known in the art, such as scanning the film and quantifying the relative pixel intensity using a computer program such as NIH Image (National Institutes of Health, Bethesda, MD), wherein the detection of hybridization of a Reg1 α -specific probe to the clinical sample is indicative of the presence of Reg1 α or TIMP1 and thus may be used to detect colorectal cancer.

[0141] In an alternate embodiment, the presence and optionally the quantity of Reg1 α or TIMP1 in a clinical sample may be determined using the Taqman™ (Perkin-Elmer, Foster City, CA) technique, which is performed with a transcript-specific antisense probe (i.e., a probe capable of specifically hybridizing to Reg1 α). This probe is specific for a Reg1 α or TIMP1 PCR product and is prepared with a quencher and fluorescent reporter probe complexed to the 5' end of the oligonucleotide. Different fluorescent markers can be attached to different reporters, allowing for measurement of two products in one reaction (e.g., measurement of Reg1 α or TIMP1 and at least one additional colorectal cancer associated marker). When Taq DNA polymerase is activated, it cleaves off the fluorescent reporters by its 5'-to-3' nucleolytic activity. The reporters, now free of the quenchers, fluoresce. The color change is proportional to the amount of each specific product and is measured by fluorometer; therefore, the amount of each color can be measured and the RT-PCR product can be quantified. The PCR reactions can be performed in 96 well plates so that samples derived from many individuals can be processed and measured simultaneously. The Taqman™ system has the additional advantage of not requiring gel electrophoresis and allows for quantification when used with a standard curve.

Screening for polypeptide molecules

[0142] The Reg1 α - or TIMP1-specific and colorectal cancer marker-specific antibodies described above may be used to detect the presence of Reg1 α or TIMP1 or an additional colorectal cancer associated marker in a clinical sample by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitation reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e. g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0143] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA

buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e. g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e. g., 1-4 hours) at 4 C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4 C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. In the case of immunoprecipitation of a serum sample, however the above protocol is carried out absent the cell lysis step. The ability of the antibody to immunoprecipitate Reg1 α or TIMP 1 (or other colorectal cancer marker) antigen can be assessed by, e. g., western blot analysis. The parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e. g., preclearing the cell lysate with sepharose beads) are well known to those of skill in the art (Ausubel et al, *supra*).

[0144] Reg1 α or TIMP1 polypeptides, and optionally one or more additional colorectal cancer associated markers may be detected in a patient clinical sample using Western blot analysis. Briefly, Western blot analysis comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e. g., 8%-20% SDS-PAGE), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e. g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e. g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e. g., an antihuman antibody) conjugated to an enzymatic substrate (e. g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e. g., ³²P or ¹²⁵I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. Methods for the optimization of such an analysis are well known in the art (Ausubel, et al., *supra*).

[0145] Alternatively, the presence of Reg1 α or TIMP1 and optionally one or more additional colorectal cancer associated markers in a clinical sample may be detected by ELISA. ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate (or other suitable container) with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e. g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest, that is, the antibody which will bind to Reg1 α or TIMP1 or a second colorectal cancer associated marker) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. This method may be modified or optimized according techniques which are known to those of skill in the art.

[0146] The binding affinity of an antibody to an antigen and the off-rate of an antibodyantigen interaction can be determined by competitive binding assays. One example of such an assay is a radioimmunoassay comprising the incubation of labeled antigen (e. g., Reg1 α labeled with ³H or ¹²⁵I) with an anti-Reg1 α or TIMP1 antibody in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e. g., ³H or ¹²⁵I) in the presence of increasing amounts of an unlabeled second antibody.

[0147] Preferably, the above detection assays re be carried out using antibodies to detect the protein product encoded by a nucleic acid having the sequence of SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto. Preferably, the protein product has the sequence of one or more of SEQ ID Nos. 2, 4, or 100. In addition, the above detection assays may be conducted using one or more antibodies which specifically recognize and bind to at least one additional colorectal cancer associated marker. Accordingly, in one embodiment, the assay would include contacting the proteins of the test cell with an antibody specific for the gene product of a nucleic acid represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto, and determining the approximate amount of immunocomplex formation by the antibody and the proteins of the test cell, wherein a detection of such an immunocomplex is indicative of the presence of the antigen, and thus, permits the detection of colorectal cancer.

[0148] Immunoassays, useful in the present invention include those described above, and can also include both homogeneous and heterogeneous procedures such as fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (EIA), and nephelometric inhibition immunoassay (NIA).

[0149] In another embodiment, the level of the encoded product, i.e., the product encoded by SEQ ID Nos 1, 3 or 33, or a sequence complementary thereto, in a biological fluid (e.g., blood or urine) of a patient may be determined as a way of monitoring the level of expression of the marker nucleic acid sequence in cells of that patient. Such a method would include the steps of obtaining a sample of a biological fluid from the patient, contacting the sample (or proteins from the sample) with an antibody specific for a encoded marker polypeptide, and determining the amount of immune complex formation by the antibody, with the amount of immune complex formation being indicative of the level of the

marker encoded product in the sample. This determination is particularly instructive when compared to the amount of immune complex formation by the same antibody in a control sample taken from a normal individual or in one or more samples previously or subsequently obtained from the same person.

[0150] In another embodiment, the method can be used to determine the amount of marker polypeptide present in a cell, which in turn can be correlated with progression of a hyperproliferative disorder, e.g., colorectal cancer. The level of the marker polypeptide can be used predictively to evaluate whether a sample of cells contains cells which are, or are predisposed towards becoming, transformed cells. Moreover, the subject method can be used to assess the phenotype of cells which are known to be transformed, the phenotyping results being useful in planning a particular therapeutic regimen. For instance, very high levels of the marker polypeptide in sample cells is a powerful diagnostic and prognostic marker for a cancer, such as colorectal cancer. The observation of marker polypeptide level can be utilized in decisions regarding, e.g., the use of more aggressive therapies.

[0151] As set out above, one aspect of the present invention relates to detection assays for determining, in the context of cells isolated from a patient, if the level of a marker polypeptide is significantly reduced in the sample cells. The term "significantly reduced" refers to a cell phenotype wherein the cell possesses a reduced cellular amount of the marker polypeptide relative to a normal cell of similar tissue origin. For example, a cell may have less than about 50%, 25%, 10%, or 5% of the marker polypeptide that a normal control cell. In particular, the assay evaluates the level of marker polypeptide in the test cells, and, preferably, compares the measured level with marker polypeptide detected in at least one control cell, e.g., a normal cell and/or a transformed cell of known phenotype.

[0152] Of particular importance to the subject invention is the ability to quantitate the level of normal or abnormal Reg1 α or TIMP1 expression. The expression of Reg1 α or TIMP1, and/or the level of expression of Reg1 α or TIMP1 can be used predictively to evaluate whether a patient is predisposed towards developing colorectal cancer, or for determining the severity of colorectal cancer.

[0153] In one embodiment, tissue samples may be used to measure Reg1 α or TIMP1 expression by immunohistochemical staining which may be used to determine the number of cells (i.e., colon cells) expressing Reg1 α or TIMP1. For such staining, a multiblock of tissue is taken from the biopsy or other tissue sample and subjected to proteolytic hydrolysis, employing such agents as protease K or pepsin. In certain embodiments, it may be desirable to isolate a nuclear fraction from the sample cells and detect the level of the marker polypeptide in the nuclear fraction.

[0154] The tissue samples are fixed by treatment with a reagent such as formalin, glutaraldehyde, methanol, or the like. The samples are then incubated with an antibody, preferably a monoclonal antibody, with binding specificity for Reg1 α or TIMP1 and optionally an additional colorectal cancer associated marker. This antibody may be conjugated to a label for subsequent detection of binding. Samples are incubated for a time sufficient for formation of the immunocomplexes. Binding of the antibody is then detected by virtue of a label conjugated to this antibody. Where the antibody is unlabeled, a second labeled antibody may be employed, e.g., which is specific for the isotype of the anti-marker polypeptide antibody. Examples of labels which may be employed include radionuclides, fluorescers, chemiluminescers, enzymes and the like.

[0155] Where enzymes are employed, the substrate for the enzyme may be added to the samples to provide a colored or fluorescent product. Examples of suitable enzymes for use in conjugates include horseradish peroxidase, alkaline phosphatase, malate dehydrogenase and the like. Where not commercially available, such antibody-enzyme conjugates are readily produced by techniques known to those skilled in the art. Other assays, known to those of skill in the art for determining the presence and/or quantity of a polypeptide in a sample (either serum or tissue) are also encompassed by the present invention.

Drug screening

[0156] Several in vivo methods can be used to identify compounds that modulate expression of Reg1 α or TIMP1 nucleic acids (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) and/or alter for example, inhibit the bioactivity of the encoded polypeptide (e.g., SEQ ID Nos: 2, 4, or 100).

[0157] Drug screening is performed by adding a test compound to a sample of cells, and monitoring the effect. A parallel sample which does not receive the test compound is also monitored as a control. The treated and untreated cells are then compared by any suitable phenotypic criteria, including but not limited to microscopic analysis, viability testing, ability to replicate, histological examination, the level of a particular RNA or polypeptide associated with the cells, the level of enzymatic activity expressed by the cells or cell lysates, and the ability of the cells to interact with other cells or compounds. Differences between treated and untreated cells indicates effects attributable to the test compound.

[0158] Desirable effects of a test compound include an effect on any phenotype that was conferred by the cancer-associated marker nucleic acid sequence. Examples include a test compound that limits the overabundance of mRNA, limits production of the encoded protein, or limits the functional effect of the protein. The effect of the test compound would be apparent when comparing results between treated and untreated cells.

[0159] The invention thus also encompasses methods of screening for agents which inhibit expression of Reg1 α or TIMP1 nucleic acid (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) *in vitro*, comprising exposing either a cell or tissue in which Reg1 α or TIMP1 nucleic acid mRNA is detectable or cultured cells comprising and capable of expressing Reg1 α or TIMP1 nucleic acid to an agent in order to determine whether the agent is capable of inhibiting production of the mRNA; and determining the level of mRNA in the exposed cells or tissue, wherein a decrease in the level of the mRNA after exposure of the cell line to the agent is indicative of inhibition of the marker nucleic acid mRNA production.

[0160] Alternatively, the screening method may include *in vitro* screening of a cell or tissue in which Reg1 α or TIMP1 is detectable, or cultured cells which express Reg1 α or TIMP1, to an agent suspected of inhibiting production of Reg1 α or TIMP1 protein; and determining the level of the Reg1 α or TIMP1 protein in the cells or tissue, wherein a decrease in the level of marker protein after exposure of the cells or tissue to the agent is indicative of inhibition of marker protein production.

[0161] The invention also encompasses *in vivo* methods of screening for agents which inhibit expression of the marker nucleic acids, comprising exposing a mammal having tumor cells or serum in which Reg1 α or TIMP1 mRNA or protein is detectable to an agent suspected of inhibiting production of marker mRNA or protein; and determining the level of marker mRNA or protein in serum or tumor cells of the exposed mammal. A decrease in the level of marker mRNA or protein after exposure of the mammal to the agent is indicative of inhibition of marker nucleic acid expression. Optionally, the effect of the candidate agent on the expression of at least one additional colorectal cancer associated marker may also be determined.

[0162] Accordingly, the invention provides a method comprising incubating a cell expressing the marker nucleic acids (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) with a test compound and measuring the mRNA or protein level. The invention further provides a method for quantitatively determining the level of expression of the marker nucleic acids in a cell population or clinical sample, and a method for determining whether an agent is capable of increasing or decreasing the level of expression of the Reg1 α or TIMP1 nucleic acid in a cell population or clinical sample. The method for determining whether an agent is capable of increasing or decreasing the level of expression of Reg1 α or TIMP1 nucleic acid in a cell population comprises the steps of (a) preparing cell extracts from control and agent-treated cell populations, (b) isolating the Reg1 α or TIMP1 polypeptide from the cell extracts, (c) quantifying (e.g., in parallel) the amount of an immunocomplex formed between Reg1 α or TIMP1 polypeptide and an antibody specific to said polypeptide. The Reg1 α or TIMP1 polypeptide of this invention may also be quantified by assaying for its bioactivity. Agents that induce an increase in Reg1 α or TIMP1 nucleic acid expression may be identified by their ability to increase the amount of immunocomplex formed in the treated cell as compared with the amount of the immunocomplex formed in the control cell. In a similar manner, agents that decrease expression of Reg1 α or TIMP1 nucleic acid may be identified by their ability to decrease the amount of the immunocomplex formed in the treated cell extract as compared to the control cell.

[0163] mRNA levels can be determined by Northern blot hybridization. mRNA levels can also be determined by methods involving PCR. Other sensitive methods for measuring mRNA, which can be used in high throughput assays, e.g., a method using a DELFIA endpoint detection and quantification method, are described, e.g., in Webb and Hurskainen (1996) *Journal of Biomolecular Screening* 1:119. Reg1 α protein levels can be determined by immunoprecipitations or immunohistochemistry using an antibody that specifically recognizes the protein product of SEQ ID Nos: 2, 4, or 100.

[0164] Agents that are identified as active in the drug screening assay are candidates to be tested for their capacity to block cell proliferation activity. These agents would be useful for treating a disorder involving aberrant growth of cells, especially colon cells, especially colorectal cancer.

[0165] A variety of assay formats will suffice and, in light of the present disclosure, those not expressly described herein will nevertheless be comprehended by one of ordinary skill in the art. For instance, the assay can be generated in many different formats, and include assays based on cell-free systems, e.g., purified proteins or cell lysates, as well as cell-based assays which utilize intact cells.

[0166] In many drug screening programs which test libraries of compounds and natural extracts, high throughput assays are desirable in order to maximize the number of compounds surveyed in a given period of time. Assays of the present invention which are performed in cell-free systems, such as may be derived with purified or semi-purified proteins or with lysates, or with proteins purified or semi-purified from serum, are often preferred as "primary" screens in that they can be generated to permit rapid development and relatively easy detection of an alteration in a molecular target which is mediated by a test compound. Moreover, the effects of cellular toxicity and/or bioavailability of the test compound can be generally ignored in the *in vitro* system, the assay instead being focused primarily on the effect of the drug on the molecular target as may be manifest in an alteration of binding affinity with other proteins or changes in enzymatic properties of the molecular target.

EXAMPLES

[0167] The examples below are non-limiting and are merely representative of various aspects and features of the present invention.

Example 1: Generation of anti- Reg1 α antibodies

[0168] To generate antibodies to Reg1 α , the full-length open reading frame of Reg1 α (shown in either SEQ ID NO: 1 or 3) was directionally cloned into a mammalian expression vector, such as pcDNA3.1/V5-His (Invitrogen), which includes C-terminal epitope and purification tags. The insert sequence was verified by dideoxy sequencing (see, for example, Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley and Sons). Recombinant fusion protein was produced in a transient expression system in mammalian cells (e.g. CHO cells). The recombinant protein was purified from the cell culture supernatants by immobilized metal affinity chromatography (IMAC) by utilizing the C terminal His-tag. The sequence of the Reg1 α protein used for the production of antibodies of the present invention is shown in either of SEQ ID Nos 2 or 4, all of which represent a functional Reg1 α protein, and which are encoded by SEQ ID Nos 1 or 3, respectively. The purified, recombinant Reg1 α protein was emulsified in Freund's adjuvant and injected into rabbits. The animals were periodically boosted until they elicited a reasonable serum titer of specific antibody to Reg1 α . Methods for antibody production are well known to those of skill in the art and may be found, for example, in Harlow et al. *Antibodies: A laboratory manual*, 1988, Cold Spring Harbor Laboratory. The polyclonal antibodies, which recognized both native and denatured Reg1 α , were utilized to develop a microtiter-based ELISA assay. Methods of performing an ELISA assay are well known to those of skill in the art (see, for example, Ausubel et al., *supra*).

Example 2: Detection of Reg1 α in Colorectal cancer Patient Serum Samples

[0169] The present invention relates to a method for the detection of colorectal cancer in an individual, which method includes the detection of Reg1 α polypeptides in a serum sample from an individual with colorectal cancer, wherein the detection of Reg1 α is indicative of the presence of colorectal cancer. Accordingly, Reg1 α expression was measured in serum samples obtained from patients having been diagnosed with colorectal cancer.

[0170] All patients used in this study were diagnosed at their respective medical institutions by qualified physicians using conventional diagnostic means, including physical exam, blood analysis, imaging, and endoscopy. Once identified, patients provided informed consent through an IRB approved protocol. The severity of colorectal cancer in each patient was graded using the Dukes staging scheme. Serum samples were subsequently collected from each patient using methods known to those of skill in the art. Samples were subsequently assessed for the presence of Reg1 α by the ELISA assay described above. Figure 1 shows the levels of Reg1 α protein measured in the colorectal cancer patients compared to samples obtained from naive patients and additional patients diagnosed with either inflammatory bowel disease (IBD) or cirrhosis of the liver. Figure 2 shows the levels of Reg1 α expression in the colorectal cancer patients of Figure 1, identified at each stage of colorectal cancer severity. As can be seen in Figures 1 and 2, Reg1 α expression is clearly elevated in serum samples obtained from patients diagnosed with colorectal cancer, and therefore may be used to detect the presence of colorectal cancer in a patient.

Example 3: Detection of Reg1 α Nucleic Acid Sequence in Colorectal cancer

[0171] In one embodiment, the present invention provides for a method of detecting the presence of colorectal cancer in a patient by detecting the presence of nucleic acid molecules encoding Reg1 α in a serum sample obtained from a patient.

[0172] Serum may be obtained from a patient suspected of having colorectal cancer by methods described above and known to those of skill in the art. Nucleic acid molecules encoding Reg1 α may be detected, for example, by Northern analysis. Briefly, probes for detection of Reg1 α mRNA in a patient sample are derived by amplifying the Reg1 α coding sequence by RT-PCR according to techniques known in the art. The cDNA fragments generated in this manner are subsequently cloned into a PCRII vector using the TA cloning kit (Invitrogen). The identity of each fragment can be verified by sequencing in each direction from the T3 and T7 polymerase sites present in the cloning vector. The cDNA molecules produced in this manner are then used to produce ³²P-labeled Reg1 α cDNA probes using, for example, the Prime-It kit from Stratagene. Subsequently, 5 to 10 μ g of total RNA isolated from the serum of a patient suspected of having colorectal cancer is separated on an agarose/formaldehyde gel in 1X MOPS buffer. Methods of isolating RNA from a patient sample such as serum are well known in the art (see, for example, Ausubel et al., *supra*). Following staining with ethidium bromide and visualization under ultra violet light to determine the integrity of the RNA, the RNA is hydrolyzed by treatment with 0.05M NaOH/1.5M NaCl followed by incubation with 0.5M Tris-Cl (pH 7.4)/1.5M NaCl. The RNA is transferred to a commercially available nylon or nitrocellulose membrane (e.g. Hybond-N membrane,

Amersham, Arlington Heights, IL) by methods well known in the art (Ausubel et al., *supra*, Sambrook et al., *supra*). Following transfer and UV cross linking, the membrane is hybridized with a ³²P-labeled Reg1α cDNA probe in hybridization solution (e.g. in 50% formamide/2.5% Denhardt's/100-200mg denatured salmon sperm DNA/0.1% SDS/5X SSPE) overnight at 65°C. The hybridization conditions can be varied as necessary as described in Ausubel et al., *supra* and Sambrook et al., *supra*. Following hybridization, the membrane is washed at room temperature in 2X SSC/0.1% SDS, at 42°C in 1X SSC/0.1% SDS, at 65°C in 0.2X SSC/0.1% SDS, and exposed to film overnight with an intensifying screen at -80° C. The stringency of the wash buffers can also be varied depending on the amount of background signal (Ausubel et al., *supra*). The film is subsequently developed and the intensity bands corresponding to the radiolabeled probe hybridized to RNA are quantified using methods known to those of skill in the art, for example, by digitizing the film and analyzing the band intensity with a computer software program such as NIH Image (NIH, Bethesda, MD).

[0173] Alternatively, Reg1α mRNA may be detected in a patient sample by real-time amplification using oligonucleotide primers capable of specifically hybridizing to the Reg1α sequence. For example, real-time PCR and TaqMan® probes may be used to detect and quantitate the presence of Reg1α mRNA in a patient sample. The technique of real-time PCR is well known in the art (see, for example, U.S. Pat. Nos. 5,691,146; 5,779,977; 5,866,336; and 5,914,230). Methods of designing primers useful for the amplification of Reg1α sequences are well known in the art (see, for example, Ausubel et al., *supra*).

[0174] cDNA samples, reverse transcribed from mRNA obtained from patient serum samples may be used to generate PCR products via an ABI 7700 sequence detection system (Applied Biosystems, Foster City, CA). A measurement may then be made of the level of expression of Reg1α in the patient sample to determine if Reg1α mRNA levels are elevated, thus, providing a means for the detection of colorectal cancer in the patient.

Example 4: Detection of Reg1α in Other Patient Samples

[0175] In one embodiment of the present invention, colorectal cancer may be detected in a patient by detecting the expression of Reg1α in a clinical patient sample, which is not a serum sample. For example, a circulating cell sample may be obtained from a patient by collecting a sample such as blood, stool, or other bodily fluid. The sample is then subsequently treated to lyse the cells present therein, for example by treating the sample with a suitable lysis buffer, such as a buffer containing 30 mM Tris-Cl, pH 7.4, 100 mM NaCl, 5 mM EDTA, 1% (w/v) SDS, and 100 µg/ml proteinase K (for isolation of nucleic acid). The resulting sample is then analyzed for Reg1α expression either by isolating total RNA from the sample, as described above, and in Ausubel et al., *supra*, or the sample may be separated on a polyacrylamide gel for analysis by Western blot, or may be utilized in an ELISA-based assay as described above in Example 2.

Example 5. Detection of TIMP1 in patient serum samples

[0176] The present invention provides for the detection and monitoring of colorectal cancer in a patient by measuring the level of TIMP 1 polypeptide in a patient sample, preferably in a plasma sample. TIMP 1 expression was determined in 63 samples from patients diagnosed with colorectal cancer relative to the expression level of TIMP1 in 35 healthy individuals. The results demonstrate that TIMP1, in addition to one or more other colorectal cancer associated markers is overexpressed in colorectal cancer samples relative to normal samples, thus indicating that TIMP1 is a valuable marker for the detection of colorectal cancer in a patient (Figure 3).

[0177] To assess TIMP 1 polypeptide expression levels, 63 pre-treatment plasma samples from patients with colorectal cancer, and 35 samples from healthy donors were tested in either commercially available ELISAs (Osteopontin), ADVIA Centaur Immunoassays (CEA and Ferritin), or in-house developed ELISA (TIMP1). All patients used in this study were diagnosed at their respective medical institutions by qualified physicians using conventional diagnostic means, including physical exam, blood analysis, imaging, or endoscopy. Once identified, patients provided informed consent through an IRB approved protocol. The extent of colorectal cancer in each patient was determined using the Dukes' staging scheme. Serum and plasma samples were subsequently collected from each patient using methods known to those of skill in the art.

[0178] Specificity at appropriate cutoff values was determined for each marker (e.g., TIMP1, osteopontin, CEA, and ferritin) by evaluating the normal samples. For example, the 100% specificity cutoff for any given marker is equal to the marker value of the highest normal sample. Using these values as the cutoffs, the levels of each marker in the 63 cancer samples were compared to their own respective cutoff values. If the level in the cancer sample was higher than the determined cutoff value, the sample was deemed "positive" and is represented by a shaded box (Figure 3). This same process was repeated at 97% specificity (using the second highest normal; e.g., 34 of the 35 samples were equal to or below this value). The overall specificity level for the entire panel is calculated by multiplying the specificity of each marker in the panel (e.g., 97% x 97% x 97% x 97% = 89% specificity for the panel). The markers were arranged

on the graphs shown in Figure 3, according to the frequency of their overexpression in the cancer samples (TIMP1 was overexpressed in the highest number of cancer patients and is therefore listed first). The marker adding the most to the sensitivity of TIMP 1 is ranked second. For example, the 57% sensitivity/100% specificity graph shows that TIMP1 was elevated in 19 of the 63 colorectal cancer patient plasma samples, and is thus listed first on the graph.
 5 Evaluating the samples for osteopontin yielded seven additional positive patient samples, and osteopontin is thus listed second on the graph.

[0179] The sensitivity of the panel was determined by dividing the cumulative number of samples that were positive for at least one marker by the total number of cancer samples (63). Other embodiments will be evident to those of skill in the art. It should be understood that the foregoing detailed description is provided for clarity only and is merely
 10 exemplary. The spirit and scope of the present invention are not limited to the above examples, but are encompassed by the following claims.

15

20

25

30

35

40

45

50

55

EP 1 439 393 A2

SEQUENCE LISTING

5 <110> Bayer Healthcare, LLC et al.

<120> REG1A

10

<130> 1657/2011B

15

<160> 138

20

<170> FastSEQ for Windows Version 4.0

25 <210> 1

<211> 777

<212> DNA

30 <213> Homo sapiens

<400> 1

35 ttcttcaaac cctcctcttc cctgtgttct cctacagaga ttgctgattt ctccttaagc 60

aagagattca ctgccgctaa gcatggctca gaccaactcg ttcttcattg tgatctctc

120

40 cctgatgttc ctgtctctga gccaaaggcca agaggcccag acagagttgc ccaggcccg

180

gatcagctgc ccagaaggca ccaatgccta tcgctcctac tgctactact ttaatgaaga

240

45 ccgtgagacc tgggttgatg cagatctcta ttgccagaac atgaattcgg gcaacctggt

300

50 gtctgtgctc acccaggccg aggggtgcctt tgtggcctca ctgattaagg agagtggcac

360

tgatgacttc aatgtctgga ttggcctcca tgaccccaaa aagaaccgcc gctggcactg

420

55 gagcagtggg tccctgggtc cctacaagtc ctggggcatt ggagcccaaa gcagtgttaa

480

EP 1 439 393 A2

tcctggctac tgtgtgagcc tgacctcaag cacaggattc cagaaatgga aggatgtgcc
 540
 5 ttgtgaagac aagttctcct ttgtatgcaa gttcaaaaac tagaggcagc tggaaaatac
 600
 atgtctagaa ctgatccagc aattacaacg gagtcaaaaa ttaaaccgga ccattctctcc
 660
 10 aactcaactc aacctggaca ctctcttctc tgctgagttt gccttggtta tcttcaatag
 720
 ttttacctac cccagtcttt ggaaccctaa ataataaaaa taaacatggt ttccact
 15 777

 <210> 2
 20 <211> 166
 <212> PRT
 25 <213> Homo sapiens

 <400> 2
 30 Met Ala Gln Thr Asn Ser Phe Phe Met Leu Ile Ser Ser Leu Met Phe
 1 5 10 15
 Leu Ser Leu Ser Gln Gly Gln Glu Ala Gln Thr Glu Leu Pro Gln Ala
 35 20 25 30
 Arg Ile Ser Cys Pro Glu Gly Thr Asn Ala Tyr Arg Ser Tyr Cys Tyr
 40 35 40 45
 Tyr Phe Asn Glu Asp Arg Glu Thr Trp Val Asp Ala Asp Leu Tyr Cys
 50 55 60
 45 Gln Asn Met Asn Ser Gly Asn Leu Val Ser Val Leu Thr Gln Ala Glu
 65 70 75 80
 Gly Ala Phe Val Ala Ser Leu Ile Lys Glu Ser Gly Thr Asp Asp Phe
 50 85 90 95
 Asn Val Trp Ile Gly Leu His Asp Pro Lys Lys Asn Arg Arg Trp His
 55 100 105 110

EP 1 439 393 A2

Trp Ser Ser Gly Ser Leu Val Ser Tyr Lys Ser Trp Gly Ile Gly Ala
 115 120 125
 5 Pro Ser Ser Val Asn Pro Gly Tyr Cys Val Ser Leu Thr Ser Ser Thr
 130 135 140
 10 Gly Phe Gln Lys Trp Lys Asp Val Pro Cys Glu Asp Lys Phe Ser Phe
 145 150 155 160
 Val Cys Lys Phe Lys Asn
 15 165
 20
 <210> 3
 <211> 749
 25 <212> DNA
 <213> Homo sapiens
 30
 <400> 3
 agccaacaga gattgttgat ttgcctctta agcaagagat tcattgcagc tcagcatggc 60
 35 tcagaccagc tcatacttca tgctgatctc ctgcctgatg tttctgtctc agagccaagg
 120
 ccaagaggcc cagacagagt tgccccaggc ccggatcagc tgcccagaag gcaccaatgc
 180
 40 ctatcgctcc tactgctact actttaatga agaccgtgag acctgggttg atgcagatct
 240
 ctattgccag aacatgaatt cgggcaacct ggtgtctgtg ctcacccagg ccgaggggtgc
 45 300
 ctttgtggcc tactgatta aggagagtgg cactgatgac ttcaatgtct ggattggcct
 360
 50 ccatgacccc aaaaagaacc gccgctggca ctggagcagt gggtccttg tctcctacaa
 420
 gtctctggggc attggagccc caagcagtgt taatcctggc tactgtgtga gcctgacctc
 480
 55

EP 1 439 393 A2

aagcacagga ttccagaaat ggaaggatgt gccttgtgaa gacaagttct cctttgtctg
540

5 caagttcaaa aactagaggc agctggaaaa tacatgtcta gaactgatcc agcaattaca
600

acggagtcaa aaattaaacc ggaccatctc tccaactcaa ctcaacctgg acactctctt
660

10 ctctgctgag tttagccttg taatcttcaa tagttttacc taccacagtc ttggaacct
720

taaataataa aaataaacat gtttcact
15 749

<210> 4

20 <211> 166

<212> PRT

25 <213> Homo sapiens

<400> 4

30 Met Ala Gln Thr Ser Ser Tyr Phe Met Leu Ile Ser Cys Leu Met Phe
1 5 10 15

35 Leu Ser Gln Ser Gln Gly Gln Glu Ala Gln Thr Glu Leu Pro Gln Ala
20 25 30

Arg Ile Ser Cys Pro Glu Gly Thr Asn Ala Tyr Arg Ser Tyr Cys Tyr
40 35 40 45

Tyr Phe Asn Glu Asp Arg Glu Thr Trp Val Asp Ala Asp Leu Tyr Cys
50 55 60

45 Gln Asn Met Asn Ser Gly Asn Leu Val Ser Val Leu Thr Gln Ala Glu
65 70 75 80

50 Gly Ala Phe Val Ala Ser Leu Ile Lys Glu Ser Gly Thr Asp Asp Phe
85 90 95

Asn Val Trp Ile Gly Leu His Asp Pro Lys Lys Asn Arg Arg Trp His
55 100 105 110

EP 1 439 393 A2

Trp Ser Ser Gly Ser Leu Val Ser Tyr Lys Ser Trp Gly Ile Gly Ala
115 120 125

5 Pro Ser Ser Val Asn Pro Gly Tyr Cys Val Ser Leu Thr Ser Ser Thr
130 135 140

10 Gly Phe Gln Lys Trp Lys Asp Val Pro Cys Glu Asp Lys Phe Ser Phe
145 150 155 160

Val Cys Lys Phe Lys Asn
15 165

20 <210> 5
<211> 2974

25 <212> DNA
<213> Homo sapiens

30 <400> 5

ctcagggcag agggaggaag gacagcagac cagacagtca cagcagcctt gacaaaacgt 60

35 tcctggaact caagctcttc tccacagagg aggacagagc agacagcaga gaccatggag
120

tctccctcgg cccctcccca cagatggtgc atcccctggc agaggctcct gctcacagcc
180

40 tcacttctaa ccttctggaa cccgcccacc actgccaaagc tcactattga atccacgccg
240

ttcaatgtcg cagaggggaa ggaggtgctt ctacttgtcc acaatctgcc ccagcatctt
45 300

tttggctaca gctggtacaa aggtgaaaga gtggatggca accgtcaaat tataggatat
360

50 gtaataggaa ctcaacaagc taccacaggg ccgcataca gtggtcgaga gataatatac
420

cccaatgcat cctgctgat ccagaacatc atccagaatg acacaggatt ctacacccta
480

55

cacgtcataa agtcagatct tgtgaatgaa gaagcaactg gccagttccg ggtataaccg
 540
 5 gagctgccc aagcctccat ctccagcaac aactccaaac ccgtggagga caaggatgct
 600
 gtggccttca cctgtgaacc tgagactcag gacgcaacct acctgtggtg ggtaaacaat
 660
 10 cagagcctcc cggtcagtcc caggctgcag ctgtccaatg gcaacaggac cctcactcta
 720
 ttcaatgtca caagaaatga cacagcaagc tacaaatgtg aaaccagaa cccagtgagt
 15 780
 gccaggcgca gtgattcagt catcctgaat gtccctctatg gcccgatgc cccaccatt
 840
 20 tcccctctaa acacatctta cagatcaggg gaaaatctga acctctcctg ccacgcagcc
 900
 tctaaccac ctgcacagta ctcttggtt gtcaatggga ctttcagca atccaccaa
 960
 25 gagctcttta tcccaacat cactgtgaat aatagtggat cctatacgtg ccaagccat
 1020
 aactcagaca ctggcctcaa taggaccaca gtcacgacga tcacagtcta tgcagagcca
 1080
 30 cccaaaccct tcatcaccag caacaactcc aacccgtgg aggatgagga tgctgtagcc
 1140
 ttaacctgtg aacctgagat tcagaacaca acctacctgt ggtgggtaaa taatcagagc
 35 1200
 ctcccgtca gtcccaggct gcagctgtcc aatgacaaca ggaccctcac tctactcagt
 1260
 40 gtcacaagga atgatgtagg accctatgag tgtggaatcc agaacgaatt aagtgttgac
 1320
 cacagcgacc cagtcacct gaatgtcctc tatggcccag acgacccac catttcccc
 1380
 45 tcatacacct attaccgtcc aggggtgaac ctacgcctct cctgccatgc agcctctaac
 1440
 ccacctgcac agtattcttg gctgattgat gggaacatcc agcaacacac acaagagctc
 50 1500
 tttatctcca acatcactga gaagaacagc ggactctata cctgccaggc caataactca
 1560
 55 gccagtggcc acagcaggac tacagtcaag acaatcacag tctctgcgga gctgccaag
 1620

ccctccatct ccagcaacaa ctccaaaccc gtggaggaca aggatgctgt ggccttcacc
 1680

5 tgtgaacctg aggctcagaa cacaacctac ctgtggtggg taaatggtca gagcctccca
 1740

gtcagtccca ggctgcagct gtccaatggc aacaggaccc tcaactctatt caatgtcaca
 1800

10 agaaatgacg caagagccta tgtatgtgga atccagaact cagtgaagtgc aaaccgcagt
 1860

gaccagtcga ccttgatgt cctctatggg ccggacaccc ccatcatttc cccccagac
 1920

15 tcgtcttacc ttctgggagc gaacctcaac ctctcctgcc actcggcctc taacccatcc
 1980

ccgcagtatt cttggcgtat caatgggata ccgcagcaac acacacaagt tctctttatc
 2040

gccaaaaatca cgccaaataa taacgggacc tatgcctggt ttgtctctaa cttggctact
 2100

25 ggccgcaata attccatagt caagagcatc acagtctctg catctggaac ttctcctggt
 2160

ctctcagctg gggccactgt cggcatcatg attggagtgc tggttggggt tgctctgata
 2220

30 tagcagccct ggtgtagttt cttcatttca ggaagactga cagttgtttt gcttcttct
 2280

taaagcattt gcaacagcta cagtctaaaa ttgcttcttt accaaggata ttacagaaa
 2340

agactctgac cagagatcga gaccatccta gccaacatcg tgaaacccca tctctactaa
 2400

40 aaatacaaaa atgagctggg cttggtggcg cgcacctgta gtcccagtta ctcgaggagc
 2460

tgaggcagga gaatcgcttg aaccgggag gtggagattg cagtgaagccc agatcgacc
 2520

45 actgcactcc agtctggcaa cagagcaaga ctccatctca aaaagaaaag aaaagaagac
 2580

tctgacctgt actcttgaat acaagtttct gataccactg cactgtctga gaatttccaa
 2640

aactttaatg aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa
 2700

55 taattaattt catgggacta aatgaactaa tgaggattgc tgattcttta aatgtcttgt
 2760

ttcccagatt tcaggaaact ttttttcttt taagctatcc actcttacag caatttgata
2820

5 aaatatactt ttgtgaacaa aaattgagac atttacattt tctccctatg tggctcgtcc
2880

agacttggga aactattcat gaatatttat attgtatggg aatatagtta ttgcacaagt
2940

10 tcaataaaaa tctgctcttt gtataacaga aaaa
2974

15 <210> 6

<211> 2032

20 <212> DNA

<213> Homo sapiens

25 <400> 6

tccatattgt gcttccacca ctgccaataa caaaataact agcaaccatg aagtgggtgg 60

30 aatcaatttt ttttaatttt ctactaaatt ttactgaatc cagaacactg catagaaatg
120

aatatggaat agcttccata ttggattctt accaatgtac tgcagagata agtttagctg
180

35 acctggctac catatTTTTT gccagtttg ttcaagaagc cacttacaag gaagtaagca
240

aaatggtgaa agatgcattg actgcaattg agaaaccac tggagatgaa cagtcttcag
300

40 ggtgtttaga aaaccagcta cctgcctttc tggaagaact ttgcatgag aaagaaattt
360

tggaagaagta cggacattca gactgctgca gccaaagtga agagggaaga cataactgtt
420

45 ttcttgcaca caaaaagccc actccagcat cgatccact tttccaagtt ccagaacctg
480

50 tcacaagctg tgaagcatat gaagaagaca gggagacatt catgaacaaa ttcatttatg
540

agatagcaag aaggcatccc ttctgtatg cacctacaat tcttctttgg gctgctcgtc
600

55

atgacaaaat aattccatct tgctgcaaag ctgaaaatgc agttgaatgc ttccaaacaa
 660

5 aggcagcaac agttacaaaa gaattaagag aaagcagctt gttaaataca catgcatgtg
 720

cagtaatgaa aaatdddggg acccgaactt tccaagccat aactgttact aaactgagtc
 780

10 agaagtttac caaagttaat tttactgaaa tccagaaact agtcctggat gtggcccatg
 840

15 tacatgagca ctgttgacaga ggagatgtgc tggattgtct gcaggatggg gaaaaaatca
 900

tgtcctacat atgtttctca caagacactc tgtcaaacaa aataacagaa tgctgcaaac
 960

20 tgaccacgct ggaacgtggc caatgtataa ttcacgcaga aaatgatgaa aaacctgaag
 1020

gtctatctcc aaatctaaac aggttttttag gagatagaga ttttaaccaa ttttcttcag
 1080

25 gggaaaaaaa tatcttcttg gcaagttttg ttcacgaata ttcaagaaga catcctcagc
 1140

ttgctgtctc agtaattcta agagttgcta aaggatacca ggagttattg gagaagtgtt
 1200

30 tccagactga aaacctctt gaatgccaa agaaaaggaga agaagaatta cagaaatata
 1260

35 tccaggagag ccaagcattg gcaaagcgaa gctgcggcct cttccagaaa ctaggagaat
 1320

attacttaca aaatgcgttt ctctgtgtt acacaaagaa agccccccag ctgacctcgt
 1380

40 cggagctgat ggccatcacc agaaaaatgg cagccacagc agccacttgt tgccaactca
 1440

gtgaggacaa actattggcc tgtggcgagg gagcggtga cattattatc ggacacttat
 1500

45 gtatcagaca tgaaatgact ccagtaaacc ctggtgttgg ccagtgtgc acttcttcat
 1560

atgccaacag gaggccatgc ttcagcagct tgggtgtgga tgaaacatat gtcctctctg
 1620

50 cattctctga tgacaagttc attttccata aggatctgtg ccaagctcag ggtgtagcgc
 1680

55 tgcaaacgat gaagcaagag tttctcatta acctgtgaa gcaaaagcca caaataacag
 1740

aggaacaact tgaggctgtc attgcagatt tctcaggcct gttggagaaa tgctgccaaag
 1800
 5 gccaggaaca ggaagtctgc .tttgctgaag agggacaaaa actgatttca aaaactcgtg
 1860
 ctgctttggg agtttaaatt acttcagggg aagagaagac aaaacgagtc tttcattcgg
 1920
 10 tgtgaacttt tctctttaat ttaactgat ttaacacttt ttgtgaatta atgaaatgat
 1980
 aaagactttt atgtgagatt tccttatcac agaaataaaa tatctccaaa tg
 2032
 15
 <210> 7
 20 <211> 1639
 <212> DNA
 25 <213> Homo sapiens
 <400> 7
 30 agcagagcac acaagcttct aggacaagag ccaggaagaa accaccggaa ggaaccatct 60
 cactgtgtgt aaacatgact tccaagctgg ccgtggctct ctggcgagcc ttcttgattt
 120
 35 ctgcagctct gtgtgaagggt gcagttttgc caaggagtgc taaagaactt agatgtcagt
 180
 gcataaagac atactccaaa ctttccacc ccaaatttat caaagaactg agagtgattg
 240
 40 agagtggacc aactgcgcc aacacagaaa ttattgtaaa gctttctgat ggaagagagc
 300
 tctgtctgga cccaaggaa aactgggtgc agagggttgt ggagaagttt ttgaagaggg
 360
 45 ctgagaattc ataaaaaat tcattctctg tggatccaa gaatcagtga agatgccagt
 420
 50 gaaacttcaa gcaaatctac ttcaacactt catgtattgt gtgggtctgt tgtagggttg
 480
 ccagatgcaa tacaagattc ctggttaaatt ttgaatttca gtaacaatg aatagttttt
 540
 55

cattgtacca tgaatatcc agaacatact tatatgtaaa gtattattta tttgaatcta
 600
 5 caaaaaacaa caaataattt ttaaatataa ggattttcct agatattgca cgggagaata
 660
 tacaaatagc aaaattgagc caagggccaa gagaatatcc gaactttaat ttcaggaatt
 720
 10 gaatgggttt gctagaatgt gatatttgaa gcatcacata aaaatgatgg gacaataaat
 780
 tttgccataa agtcaaattt agctggaaat cctggatttt tttctgttaa atctggcaac
 840
 15 cctagtctgc tagccaggat ccacaagtcc ttgttcact gtgccttggg tttccttta
 900
 20 tttctaagtg gaaaaagtat tagccaccat cttacctcac agtgatgttg tgaggacatg
 960
 tggaagcact ttaagttttt tcatcataac ataaattatt ttcaagtga acttattaac
 1020
 25 ctatttatta tttatgtatt tatttaagca tcaaataatt gtgcaagaat ttggaaaaat
 1080
 agaagatgaa tcattgattg aatagttata aagatgttat agtaaattta ttttatttta
 1140
 30 gatattaaat gatgttttat tagataaatt tcaatcaggg ttttagatt aaacaaagaa
 1200
 acaattgggt acccagttaa attttcattt cagataaaca acaaataatt ttttagtata
 1260
 35 agtacattat tgtttatctg aaagttttta ttgaactaac aatcctagtt tgatactccc
 1320
 40 agtccttgta ttgccagctg tgttggtagt gctgtgttga attacggaat aatgagttag
 1380
 aactattaaa acagccaaaa ctccacagtc aatattagta atttcttgct ggttgaaact
 1440
 45 tgtttattat gtacaaatag attcttataa tattatttaa atgactgcat ttttaaatac
 1500
 aaggctttat atttttaact ttaagatggt tttatgtgct ctccaaattt tttttactgt
 1560
 50 ttctgattgt atggaaatat aaaagtaaat atgaaacatt taaaatataa tttgttgta
 1620
 55 aagtaaaaaa aaaaaaaaaa
 1639

5 <210> 8
 <211> 1524
 <212> DNA
 10 <213> Homo sapiens

15 <400> 8
 gcagagcaca gcatcgtcgg gaccagactc gtctcaggcc agttgcagcc ttctcagcca 60
 aacgccgacc aaggaaaact cactaccatg agaattgcag tgatttgctt ttgcctccta
 120
 20 ggcatcacct gtgccatacc agttaaacag gctgattctg gaagttctga ggaaaagcag
 180
 ctttacaaca aatacccaga tgctgtggcc acatggctaa accctgaccc atctcagaag
 25 240
 cagaatctcc tagccccaca gacccttcca agtaagtcca acgaaagcca tgaccacatg
 300
 30 gatgatatgg atgatgaaga tgatgatgac catgtggaca gccaggactc cattgactcg
 360
 aacgactctg atgatgtaga tgacactgat gattctcacc agtctgatga gtctcaccat
 420
 35 tctgatgaat ctgatgaact ggtcactgat tttcccacgg acctgccagc aaccgaagtt
 480
 ttcactccag ttgtccccac agtagacaca tatgatggcc gaggtgatag tgtggtttat
 40 540
 ggactgaggt caaaatctaa gaagtttcgc agacctgaca tccagtaccc tgatgctaca
 600
 gacgaggaca tcacctcaca catggaaagc gaggagttga atggtgcata caaggccatc
 45 660
 cccgttgccc aggacctgaa cgcgccttct gattgggaca gccgtgggaa ggacagttat
 720
 50 gaaacgagtc agctggatga ccagagtgtc gaaaccaca gccacaagca gtccagatta
 780
 tataagcgga aagccaatga tgagagcaat gagcattccg atgtgattga tagtcaggaa
 55 840

ctttccaaag tcagccgtga attccacagc catgaatttc acagccatga agatatgctg
 900
 5 gttgtagacc ccaaaagtaa ggaagaagat aaacacctga aatttcgtat ttctcatgaa
 960
 ttagatagtg catcttctga ggtcaattaa aaggagaaaa aatacaattt ctcactttgc
 10 1020
 atttagtcaa aagaaaaaat gctttatagc aaaatgaaag agaacatgaa atgcttcttt
 1080
 15 ctcagtttat tgggtgaatg tgtatctatt tgagtctgga aataactaat gtgtttgata
 1140
 attagtttag ttgtggctt catggaaact ccctgtaaac taaaagcttc agggttatgt
 1200
 20 ctatgttcat tctatagaag aaatgcaaac tatcactgta ttttaattatt tgttattctc
 1260
 tcatgaatag aaatttatgt agaagcaaac aaaatacttt taccactta aaaagagaat
 1320
 25 ataacatttt atgtcactat aatcttttgt tttttaagtt agtgtatatt ttgttgat
 1380
 tatctttttg tgggtggaat aaatctttta tcttgaatgt aataagaatt tgggtggtgc
 30 1440
 aattgcttat ttgttttccc acggttggtcc agcaattaat aaaacataac cttttttact
 1500
 35 gcctaaaaaa aaaaaaaaaa aaaa
 1524
 40 <210> 9
 <211> 5500
 <212> DNA
 45 <213> Homo sapiens
 <400> 9
 50 gcagaccgtc gctaatgaat cttggggccg gtgtcgggcc ggggcggctt gatcggcaac 60
 taggaaaccc caggcgcaga ggccaggagc gagggcagcg aggatcagag gccaggcctt
 120
 55

cccggctgcc ggcgctcctc ggaggtcagg gcagatgagg aacatgactc tcccccttcg
 180
 5 gaggaggaag gaagtccgc tgccacctta tctctgctcc tctgcctcct ccctgttccc
 240
 agagcttttt ctctagagaa gattttgaag gcggttttg tgctgacggc caccaccat
 300
 10 catctaaaga agataaactt ggcaaatgac atgcaggttc ttcaaggcag aataattgca
 360
 gaaaatcttc aaaggaccct atctgcagat gttctgaata cctctgagaa tagagattga
 420
 15 ttattcaacc aggataccta attcaagaac tccagaaatc aggagacgga gacattttgt
 480
 cagttttgca acattggacc aaatacaatg aagtattctt gctgtgctct ggttttggct
 540
 20 gtccctgggca cagaattgct gggaagcctc tgttcgactg tcagatcccc gaggttcaga
 600
 ggacggatac agcaggaacg aaaaaacatc cgaccaaca ttattcttgt gcttaccgat
 660
 25 gatcaagatg tggagctggg gtccctgcaa gtcataaaca aaacgagaaa gattatggaa
 720
 30 catggggggg ccaccttcat caatgccttt gtgactacac ccatgtgctg cccgtcacgg
 780
 tcttccatgc tcaccgggaa gtatgtgcac aatcacaatg tctacaccaa caacgagaac
 840
 35 tgctcttccc cctcgtggca ggccatgcat gagcctcgga cttttgctgt atatcttaac
 900
 aacactggct acagaacagc cttttttgga aaatacctca atgaatataa tggcagctac
 960
 40 atccccctg ggtggcgaga atggcttgga ttaatcaaga attctcgctt ctataattac
 1020
 45 actgtttgtc gcaatggcat caaagaaaag catggatttg attatgcaaa ggactacttc
 1080
 acagacttaa tcactaacga gagcattaat tacttcaaaa tgtctaagag aatgtatccc
 1140
 50 cataggcccg ttatgatggg gatcagccac gctgcgcccc acggccccga ggactcagcc
 1200
 ccacagtttt ctaaactgta cccaatgct tcccaacaca taactcctag ttataactat
 1260
 55

gcaccaaata tggataaaca ctggattatg cagtacacag gaccaatgct gcccattcac
1320

5 atggaattta caaacattct acagcgcaaa aggctccaga ctttgatgtc agtggatgat
1380

tctgtggaga ggctgtataa catgctcgtg gagacggggg agctggagaa tacttacatc
1440

10 atttacaccg ccgaccatgg ttacatatt gggcagtttg gactgggtcaa ggggaaatcc
1500

atgccatatg actttgatat tcgtgtgcct ttttttattc gtgggtccaag tgtagaacca
1560

15 ggatcaatag tcccacagat cgttctcaac attgacttgg cccccacgat cctggatatt
1620

gctgggctcg acacacctcc tgatgtggac ggcaagtctg tcctcaaact tctggacca
1680

gaaaagccag gtaacagggt tcgaacaaac aagaaggcca aaatttggcg tgatacttc
1740

25 ctagtggaaa gaggcaaatt tctacgtaag aaggaagaat ccagcaagaa tatccaacag
1800

tcaaatact tgcccaaata tgaacgggtc aaagaactat gccagcaggc caggtaccag
1860

30 acagcctgtg aacaaccggg gcagaagtgg caatgcattg aggatacatc tggcaagctt
1920

cgaattcaca agtgtaaagg acccagtgac ctgctcacag tccggcagag cacgcggaac
1980

35 ctctacgctc gcggcttcca tgacaaagac aaagagtga gttgtaggga gtctggttac
2040

40 cgtgccagca gaagccaaag aaagagtcaa cggcaattct tgagaaacca ggggactcca
2100

aagtacaagc ccagatttgt ccatactcg cagacacgtt ccttgtccgt cgaatttgaa
2160

45 ggtgaaatat atgacataaa tctggaagaa gaagaagaat tgcaagtgtt gcaaccaaga
2220

aacattgcta agcgtcatga tgaaggccac aaggggcca gagatctcca ggcttccagt
2280

50 ggtggcaaca ggggcaggat gctggcagat agcagcaacg ccgtggggcc acctaccact
2340

gtccgagtga cacacaagtg ttttattctt cccaatgact ctatccattg tgagagagaa
2400

55

ctgtaccaat cggccagagc gtggaaggac cataaggcat acattgacaa agagattgaa
2460

5 gctctgcaag ataaaattaa gaatttaaga gaagtgagag gacatctgaa gagaaggaag
2520

cctgaggaat gtagctgcag taaacaaagc tattacaata aagagaaagg tgtaaaaaag
2580

10 caagagaaat taaagagcca tcttcaccca ttcaaggagg ctgctcagga agtagatagc
2640

aaactgcaac ttttcaagga gaacaaccgt aggaggaaga aggagaggaa ggagaagaga
2700

15 cggcagagga agggggaaga gtgcagcctg cctggcctca cttgcttcac gcatgacaac
2760

20 aaccactggc agacagcccc gttctggaac ctgggatctt tctgtgcttg cacgagttct
2820

aacaataaca cctactggtg tttgcgtaca gttaatgaga cgcataattt tcttttctgt
2880

25 gagtttgcta ctggcttttt ggagtatttt gatatgaata cagatcctta tcagctcaca
2940

aatacagtgc acacggtaga acgaggcatt ttgaatcagc tacacgtaca actaatggag
3000

30 ctcagaagct gtcaaggata taagcagtgc aaccaagac ctaagaatct tgatgttgga
3060

35 aataaagatg gaggaagcta tgacctacac agaggacagt tatgggatgg atgggaaggt
3120

taatcagccc cgtctcactg cagacatcaa ctggcaaggc ctagaggagc tacacagtgt
3180

40 gaatgaaaac atctatgagt acagacaaaa ctacagactt agtctggtgg actggactaa
3240

ttacttgaag gatttagata gagtatttgc actgctgaag agtcactatg agcaaaataa
3300

45 aacaaataag actcaaactg ctcaaagtga cgggttcttg gttgtctctg ctgagcacgc
3360

tgtgtcaatg gagatggcct ctgctgactc agatgaagac ccaaggcata aggttgggaa
3420

50 aacacctcat ttgaccttgc cagctgacct tcaaaccctg catttgaacc gaccaacatt
3480

55 aagtccagag agtaaacttg aatggaataa cgacattcca gaagttaatc atttgaattc
3540

tgaacactgg agaaaaaccg aaaaatggac ggggcatgaa gagactaatc atctggaaac
3600

5 cgatttcagt ggcgatggca tgacagagct agagctcggg cccagcccca ggctgcagcc
3660

cattcgcagg caccgaaag aacttcccca gtatggtggt cctggaaagg acatttttga
3720

10 agatcaacta tatcttcctg tgcatccga tggaaattca gttcatcaga tgttcaccat
3780

ggccaccgca gaacaccgaa gtaattccag catagcgggg aagatgttga ccaaggtgga
3840

15 gaagaatcac gaaaaggaga agtcacagca cctagaaggc agcgcctcct cttcactctc
3900

20 ctctgattag atgaaactgt taccttacc taaacacagt atttcttttt aactttttta
3960

tttgtaaact aataaaggta atcacagcca ccaacattcc aagctaccct gggtagcttt
4020

25 gtgcagtaga agctagttag catgtgagca agcgggtgag acacggagac tcatcgttat
4080

aatttactat ctgccaaag tagaaaagaa ggctggggat atttgggttg gcttggtttt
4140

30 gattttttgc ttgtttgttt gttttgtact aaaacagtat tatcttttga atatcgtagg
4200

gacataagta tatacatgtt atccaatcaa gatggctaga atgggtgcctt tctgagtgtc
4260

35 taaaacttga caccctggt aaatctttca acacacttcc actgcctgcg taatgaagtt
4320

40 ttgattcatt ttttaaccact ggaatttttc aatgccgtca ttttcagtta gatgattttg
4380

cactttgaga ttaaaatgcc atgtctattt gattagtctt atttttttat ttttacaggc
4440

45 ttatcagtct cactgttggc tgtcattgtg acaaagtcaa ataaaccccc aaggacgaca
4500

cacagtatgg atcacatatt gtttgacatt aagcttttgc cagaaaatgt tgcattgtgt
4560

50 ttacctcgac ttgctaaaat cgattagcag aaaggcatgg ctaataatgt tgggtggtgaa
4620

aataaataaa taagtaaaca aaatgaagat tgctgtctct ctctgtgcct agcctcaaag
4680

cgttcatcat acatcatacc tttaagattg ctatatTTTtg ggTtatTTTc ttgacaggag
4740

5 aaaaagatct aaagatcttt tattttcatc ttttttggtt ttcttgcat gactaagaag
4800

cttaaagtgt gataaaatat gactagtttt gaatttacac caagaacttc tcaataaaag
4860

10 aaaatcatga atgctccaca atttcaacat accacaagag aagttaattt cttaacattg
4920

tgTtctatga ttatttgtaa gaccttcacc aagtTctgat atcttttaaa gacatagtTc
15 4980

aaaattgctt ttgaaaatct gtattcttga aaatatcctt gttgtgtatt aggttttttaa
5040

20 ataccagcta aaggattacc tcaactgagtc atcagtaccc tctattcag ctccccaaga
5100

tgatgtgttt ttgcttacc taagagaggt tttcttctta ttttagata attcaagtgc
5160

25 ttagataaat tatgttttct ttaagtgttt atggtaaact cttttaaaga aaatttaata
5220

tgTtatagct gaatcttttt ggtaacttta aatctttatc atagactctg tacatatgtt
30 5280

caaattagct gcttgctga tgtgtgtatc atcggTggga tgacagaaca aacatattta
5340

35 tgatcatgaa taatgtgctt tgtaaaaaga tttcaagtta ttaggaagca tactctgttt
5400

tttaatcatg tataatatTc catgatactt ttatagaaca attctggctt caggaaagtc
5460

40 tagaagcaat atttcttcaa ataaaaggtg tttaaacttt
5500

45

<210> 10

50

<211> 1778

<212> DNA

55

<213> Homo sapiens

<400> 10

5 tagaagttta caatgaagtt tcttotaata ctgctcctgc aggcactgc ttctggagct 60
 cttccctga acagctctac aagcctggaa aaaaataatg tgctatttgg tgagagatac
 120

10 ttagaaaaat tttatggcct tgagataaac aaacttccag tgacaaaaat gaaatatagt
 180
 ggaaacttaa tgaaggaaaa aatccaagaa atgcagcact tcttgggtct gaaagtgacc
 15 240
 gggcaactgg acacatctac cctggagatg atgcacgcac ctgatgtgg agtccccgat
 300

20 ctccatcatt tcagggaat gccagggggg cccgtatgga ggaaacatta tatcacctac
 360
 agaatcaata attacacacc tgacatgaac cgtgaggatg ttgactacgc aatccggaaa
 420

25 gctttccaag tatggagtaa tgttacccc ttgaaattca gcaagattaa cacaggcatg
 480
 gctgacattt tgggtggttt tgcccgtgga gctcatggag acttccatgc tttgatggc
 30 540
 aaagggtggaa tcctagccca tgcttttgga cctggatctg gcattggagg ggatgcacat
 600

35 ttgatgagg acgaattctg gactacacat tcaggaggca caaacttgtt cctcactgct
 660
 gttcacgaga ttggccattc cttaggtctt ggccattcta gtgatccaaa ggctgtaatg
 720

40 ttccccacct acaaatatgt cgacatcaac acatttcgcc tctctgctga tgacatacgt
 780
 ggcatcagt ccctgtatgg agacccaaaa gagaaccaac gcttgccaaa tcctgacaat
 840

45 tcagaaccag ctctctgtga cccaatttg agttttgatg ctgtcactac cgtgggaaat
 900
 aagatctttt tcttcaaaga caggttcttc tggctgaagg tttctgagag accaaagacc
 50 960
 agtggttaatt taatttcttc cttatggcca accttgccat ctggcattga agctgcttat
 1020

55 gaaattgaag ccagaaatca agtttttctt tttaaagatg acaatactg gttaattagc
 1080

aatttaagac cagagccaaa ttatcccaag agcatacatt cttttggttt tcctaacttt
 1140
 5 gtgaaaaaaa ttgatgcagc tgtttttaac ccacgttttt ataggaccta cttctttgta
 1200
 gataaccagt attggaggta tgatgaaagg agacagatga tggaccctgg ttatcccaaa
 1260
 10 ctgattacca agaacttcca aggaatcggg cctaaaattg atgcagtctt ctattctaaa
 1320
 aacaaatact actatttctt ccaaggatct aaccaatttg aatatgactt cctactccaa
 1380
 15 cgtatcacca aaacactgaa aagcaatagc tggtttggtt gttagaaatg gtgtaattaa
 1440
 20 tggtttttgt tagttcactt cagcttaata agtatttatt gcatatttgc tatgtcctca
 1500
 gtgtaccact acttagagat atgtatcata aaaataaaat ctgtaaacca taggtaatga
 1560
 25 ttatataaaa tacataatat ttttcaattt tgaaaactct aattgtccat tcttgcttga
 1620
 ctctactatt aagtttgaaa atagttacct tcaaagcaag ataattctat ttgaagcatg
 1680
 30 ctctgtaagt tgcttcctaa catccttgga ctgagaaatt atacttactt ctggcataac
 1740
 taaaattaag tatatatatt ttggctcaaa taaaattg
 35 1778

 <210> 11
 40 <211> 777
 <212> DNA
 45 <213> Homo sapiens

 <400> 11
 50 ggcccccttgt ctgcagagat ggctcccaat gcttcctgcc tctgtgtgca tgtccgttcc 60
 gaggaatggg atttaatgac ctttgatgcc aaccatattg acagcgtgaa aaaaatcaaa
 120
 55

gaacatgtcc ggtctaagac caaggttcct gtgcaggacc aggttctttt gctgggctcc
 180
 5 aagatcttaa agccacggag aagcctctca tcttatggca ttgacaaaga gaagaccatc
 240
 caccttacc tgaagtgggt gaagcccagt gatgaggagc tgcccttggt tcttgtggag
 300
 10 tcaggtgatg aggcaaagag gcacctctc caggtgcgaa ggtccagctc agtggcacia
 360
 gtgaaagcaa tgatcgagac taagacgggt ataatccctg agaccagat tgtgacttgc
 420
 15 aatggaaaga gactggaaga tgggaagatg atggcagatt acggcatcag aaagggcaac
 480
 ttactcttc tggcatctta ttgtattgga gggtgaccac cctggggatg ggggtgttggc
 540
 aggggtcaaa aagcttattt cttttaatct cttactcaac gaacacatct tctgatgatt
 600
 25 tcccaaaatt aatgagaatg agatgagtag agtaagattt ggggtgggatg ggtaggatga
 660
 agtatattgc ccaactctat gtttctttga ttctaacaca attaattaag tgacatgatt
 720
 30 ttactaatg tattactgag actagtaaata aaatttttaa ggcaaaatag agcattc
 777
 35
 <210> 12
 <211> 5921
 40 <212> DNA
 <213> Homo sapiens
 45
 <400> 12
 agcagacggg agtttctcct cggggtcgga gcaggaggca cgcggagtgt gaggccacgc 60
 50 atgagcggac gctaaccctc tcccagcca caaagagtct acatgtctag ggtctagaca
 120
 tgttcagctt tgtggacctc cggctcctgc tcctcttagc ggccaccgcc ctctgacgc
 180
 55

acggccaaga ggaaggccaa gtcgagggcc aagacgaaga catcccacca atcacctgcg
 240
 5 tacagaacgg cctcaggtac catgaccgag acgtgtggaa acccgagccc tgccgcatct
 300
 gcgtctgcga caacggcaag gtgttgtgcg atgacgtgat ctgtgacgag accaagaact
 360
 10 gccccggcgc cgaagtcccc gagggcgagt gctgtcccgt ctgccccgac ggctcagagt
 420
 caccacccga ccaagaaacc accggcgctg agggacccaa gggagacact ggcccccgag
 15 480
 gcccaagggg acccgaggc cccctggcc gagatggcat ccctggacag cctggaactc
 540
 20 ccggaccccc cggaccccc ggacctccc gacccccctgg cctcggagga aactttgtc
 600
 ccagctgtc ttatggctat gatgagaaat caaccggagg aatttccgtg cctggcccca
 660
 25 tgggtccctc tggtcctcgt ggtctccctg gccccctgg tgcacctgg cccaaggct
 720
 tccaaggtcc ccctggtgag cctggcgagc ctggagcttc aggtcccatg ggtccccgag
 780
 30 gtcccccagg tccccctgga aagaatggag atgatgggga agctggaaaa cctggtcgtc
 840
 ctggtgagcg tgggcctcct gggcctcagg gtgctcgagg attgcccga acagctggcc
 35 900
 tccctggaat gaaggacac agaggtttca gtggtttgga tggtgccaag ggagatgctg
 960
 40 gtccctgctgg tcctaagggt gagcctggca gccctggtga aaatggagct cctggtcaga
 1020
 tgggcccccg tggcctgcct ggtgagagag gtcgccctgg agcccctggc cctgctggtg
 1080
 45 ctgctggaaa tgatggtgct actggtgctg ccgggcccc tggtcccacc ggccccgctg
 1140
 gtccctcctgg cttccctggt gctgttggtg ctaagggtga agctgggtcc caagggcccc
 50 1200
 gaggtctga aggtccccag ggtgtgctg gtgagcctgg cccccctggc cctgctggtg
 1260
 55 ctgctggccc tgctggaaac cctggtgctg atggacagcc tggtgctaaa ggtgccaatg
 1320

gtgctcctgg tattgctggt gctcctggct tccctgggtgc ccgaggcccc tctggacccc
 1380

5 agggccccgg cgccctcct ggtcccaagg gtaacagcgg tgaacctggt gctcctggca
 1440

gcaaaggaga cactggtgct aaggagagc ctggccctgt tgggtgtcaa ggacccccctg
 1500

10 gccctgctgg agaggaagga aagcgaggag ctcgagggtga acccggaccc actggcctgc
 1560

ccggaccccc tggcgagcgt ggtggacctg gtagccgtgg tttccctggc gcagatggtg
 15 1620

ttgctggtcc caagggtccc gctggtgaac gtggttctcc tggccccgct ggccccaaag
 1680

20 gatctcctgg tgaagctggt cgtcccgggtg aagctggtct gcctggtgcc aagggtctga
 1740

ctggaagccc tggcagccct ggtcctgatg gcaaaaactgg cccccctggt cccgccggtc
 1800

25 aagatggtcg ccccgacccc ccaggccac ctggtgcccg tggtcaggct ggtgtgatgg
 1860

gattccctgg acctaaaggt gctgctggag agccccgcaa ggctggagag cgagggtgtc
 1920

30 ccggaccccc tggcgctgtc ggtcctgctg gcaaagatgg agaggctgga gctcagggac
 1980

cccctggccc tgctggtccc gctggcgaga gaggtgaaca aggccctgct ggctcccccg
 35 2040

gattccaggg tctccctggt cctgctggtc ctccaggtga agcaggcaaa cctggtgaac
 2100

40 aggggtgttc tggagacctt ggcgccccctg gccctctgag agcaagaggc gagagaggtt
 2160

tccctggcga gcgtggtgtg caagggtccc ctggtcctgc tggaccccga ggggccaacg
 2220

45 gtgctccccg caacgatggt gctaagggtg atgctggtgc ccctggagct cccggtagcc
 2280

agggcgcccc tggccttcag ggaatgcctg gtgaacgtgg tgcagctggt cttccagggc
 50 2340

ctaagggtga cagaggatg gctggtccca aagggtgctga tggctctcct ggcaaagatg
 2400

55 gcgtccgtgg tctgaccggc cccattgggtc ctccctggccc tgctggtgcc cctggtgaca
 2460

aggggtgaaag tgggtcccagc ggccctgctg gtcccactgg agctcgtggt gcccccgag.
 2520

5 accgtggtga gcctgggtccc cccggccctg ctggctttgc tggccccct ggtgctgacg
 2580

gccaacctgg tgctaaaggc gaacctggtg atgctggtgc caaaggcgat gctgggtcccc
 2640

10 ctgggcctgc cggaccgcgt ggacccccctg gccccattgg taatgttggt gctcctggag
 2700

ccaaagggtg tcgcggcagc gctgggtcccc ctgggtgctac tggtttccct ggtgctgctg
 15 2760

gccgagtcgg tcctcctggc ccctctggaa atgctggacc ccctggccct cctggtcctg
 2820

20 ctggcaaaga aggcggcaaa ggtccccgtg gtgagactgg ccctgctgga cgtcctggtg
 2880

aagttggtcc ccctgggtccc cctggccctg ctggcgagaa aggatcccct ggtgctgatg
 2940

25 gtctgctgg tgctcctggt actcccggtc ctcaaggtat tgctggacag cgtgggtggtg
 3000

tcggcctgcc tggtcagaga ggagagagag gcttccctgg tcttcctggc ccctctggtg
 3060

30 aacctggcaa acaagggtccc tctggagcaa gtggtgaacg tgggtcccccc ggtcccatgg
 3120

gccccctgg attggctgga cccctggtg aatctggacg tgaggggggt cctgctgccg
 35 3180

aagggtcccc tggacgagac ggttctcctg gcgccaaggg tgaccgtggt gagaccggcc
 3240

40 ccgctggacc ccctggtgct cctggtgctc ctggtgcccc tggccccgtt ggccctgctg
 3300

gcaagagtgg tgatcgtggt gagactggtc ctgctggtcc cgcgggtccc gtcggccccg
 3360

45 tcggcgcccc tggccccgcc ggaccccaag gccccogtg tgacaagggt gagacaggcg
 3420

aacagggcga cagaggcata aagggtcacc gtggcttctc tggcctccag ggtccccctg.
 50 3480

gcctcctgg ctctcctggt gaacaaggtc cctctggagc ctctggtcct gctgggtcccc
 3540

55 gaggtcccc tggctctgct ggtgctcctg gcaaagatgg actcaacggt ctccctggcc
 3600

ccattggggc cctggtcct cgcggtcgca ctggtgatgc tggtoctgtt ggtccccccg
3660

5 gccctcctgg acctcctggt ccccttggtc ctcccagcgc tggtttcgac ttcagcttcc
3720

tgccccagcc acctcaagag aaggctcacg atggtggccg ctactaccgg gctgatgatg
3780

10 ccaatgtggt tcgtgaccgt gacctcgagg tggacaccac cctcaagagc ctgagccagc
3840

agatcgagaa catccggagc ccagagggaa gccgcaagaa ccccgccgc acctgccgtg
3900

15 acctcaagat gtgccactct gactggaaga gtggagagta ctggattgac cccaaccaag
3960

20 gctgcaacct ggatgccatc aaagtcttct gcaacatgga gactggtgag acctgcgtgt
4020

acccactca gccagtggt gccagaaga actggtacat cagcaagaac cccaaggaca
4080

25 agaggcatgt ctggttcggc gagagcatga ccgatggatt ccagttcgag tatggcggcc
4140

agggtccga cctgccgat gtggccatcc agctgacctt cctgcgcctg atgtccaccg
4200

30 aggcctcca gaacatcacc taccactgca agaacagcgt ggcctacatg gaccagcaga
4260

ctggcaacct caagaaggcc ctgctcctca agggctccaa cgagatcgag atccgcgccg
4320

35 agggcaacag ccgcttcacc tacagcgtca ctgtcgatgg ctgcacgagt cacaccggag
4380

40 cctggggcaa gacagtgatt gaatacaaaa ccaccaagtc ctccgcctg cccatcatcg
4440

atgtggcccc cttggacgtt ggtgccccag accaggaatt cggcttcgac gttggccctg
4500

45 tctgcttcct gtaaaactccc tccatcccaa cctggctccc tcccaccaa ccaactttcc
4560

ccccaaccg gaaacagaca agcaaccaa actgaacccc ccaaaaagcc aaaaaatggg
4620

50 agacaatttc acatggactt tggaaaatat ttttttcctt tgcattcatc tctcaaactt
4680

55 agtttttatc tttgaccaac cgaacatgac caaaaaccaa aagtgcattc aaccttacca
4740

aaaaaaaaaa aaaaaaaaaa agaataaata aataagtttt taaaaaagga agcttggtcc
 4800

5 acttgcttga agacccatgc gggggaagt ccctttctgc ccgttggtt atgaaacccc
 4860

aatgctgcc tttctgctcc tttctccaca ccccccttgg cctccccctcc actccttccc
 4920

10 aaatctgtct cccagaaga cacaggaaac aatgtattgt ctgccagca atcaaaggca
 4980

atgctcaaac acccaagtgg cccccacct cagcccgctc ctgccgccc agcaccoccc
 5040

ggccctgggg acctgggtt ctgagactgc caaagaagcc ttgccatctg gcgctcccat
 5100

20 ggctcttgca acatctcccc ttcgtttttg aggggggtcat gccgggggag ccaccagccc
 5160

ctactgggt tcggaggaga gtcaggaagg gccacgacaa agcagaaaca tcggatttgg
 5220

25 ggaacgcgtg tcatcccttg tgccgcaggc tgggcgggag agactgttct gttctgttcc
 5280

ttgtgtaact gtgttgctga aagactacct cgttcttgtc ttgatgtgtc accggggcaa
 5340

30 ctgectgggg gcggggatgg gggcagggtg gaagcggctc cccattttta taccaaagg
 5400

gctacatcta tgtgatgggt ggggtgggga gggaatcact ggtgctatag aaattgagat
 5460

gccccccag gccagcaaat gttccttttt gttcaaagtc tatttttatt ccttgatatt
 5520

40 ttttctttct tttttttttt ttttgtggat ggggacttgt gaatttttct aaagggtgcta
 5580

tttaacatgg gaggagagcg tgtgcgctcc agcccagccc gctgctcact ttccaccctc
 5640

45 tctccacctg cctctggctt ctcaggcctc tgctctccga cctctctcct ctgaaacct
 5700

cctccacagc tgcagcccat cctcccggct ccctcctagt ctgtcctgcg tcctctgtcc
 5760

ccgggtttca gagacaactt cccaaagcac aaagcagttt ttccctaggg gtgggaggaa
 5820

55 gcaaaagact ctgtacctat tttgtatgtg tataataatt tgagatgttt ttaattattt
 5880

tgattgctgg aataaagcat gtggaaatga cccaaacata a
5921

5

10

<210> 13

<211> 1804

15

<212> DNA

<213> Homo sapiens

20

<400> 13

gtatcactca gaatctggca gccagttcog tcttgacaga gttcacagca tatattggtg 60

25

gattcttgtc catagtgcac ctgctttaag aattaacgaa agcagtgta agacagtaag
120

gattcaaacc atttgccaaa aatgagtcta agtgcattta ctctcttcct ggcattgatt
180

30

ggtggtacca gtggccagta ctatgattat gattttcccc tatcaattta tgggcaatca
240

tcaccaaact gtgcaccaga atgtaactgc cctgaaagct acccaagtgc catgtactgt
300

35

gatgagctga aattgaaaag tgtaccaatg gtgcctcctg gaatcaagta tctttacctt
360

aggaataacc agattgacca tattgatgaa aaggcctttg agaattgaac tgatctgcag
420

40

tggtctattc tagatcacia ccttctagaa aactccaaga taaaagggag agttttctct
480

45

aaattgaaac aactgaagaa gctgcatata aaccacaaca acctgacaga gtctgtgggc
540

ccacttccca aatctctgga ggatctgcag cttactcata acaagatcac aaagctgggc
600

50

tcttttgaag gattggtaaa cctgaccttc atccatctcc agcacaatcg gctgaaagag
660

gatgctgttt cagctgcttt taaaggcttt aaatcactcg aataccttga cttgagcttc
720

55

aatcagatag ccagactgcc ttctggtctc cctgtctctc ttctaactct ctacttagac
 780
 5 aacaataaga tcagcaacat ccctgatgag tatttcaagc gttttaatgc attgcagtat
 840
 ctgcgtttat ctcaaacga actggctgat agtgaatac ctggaaattc tttcaatgtg
 900
 10 tcatccctgg ttgagctgga tctgtcctat aacaagctta aaaacatacc aactgtcaat
 960
 gaaaaccttg aaaactatta cctggaggtc aatcaacttg agaagtttga cataaagagc
 15 1020
 ttctgcaaga tcctggggcc attatcctac tccaagatca agcatttgcg tttggatggc
 1080
 20 aatgcgatct cagaaaccag tcttcaccg gatatgtatg aatgtctacg tgttgctaac
 1140
 gaagtcactc ttaattaata tctgtatcct ggaacaatat tttatggtta tgtttttctg
 1200
 25 tgtgtcagtt ttcatagtat ccatatttta ttactgttta ttacttccat gaattttaaa
 1260
 atctgaggga aatgttttgt aaacatttat tttttttaaa gaaaagatga aaggcaggcc
 30 1320
 tatttcatca caagaacaca cacatataca cgaatagaca tcaaactcaa tgctttatct
 1380
 35 gtaaatttag tgttttttta tttctactgt caaatgatgt gcaaacctt ttactggttg
 1440
 catggaaatc agccaagttt tataatcctt aaatcttaat gttcctcaaa gcttgatta
 1500
 40 aatacatatg gatgttactc tcttgacca aattatcttg atacattcaa atttgtctgy
 1560
 ttaaaaaata ggtggtagat attgaggcca agaattattgc aaaatacatg aagcttcag
 1620
 45 cacttaaaga agtattttta gaataagaat ttgcatactt acctagtga acttttctag
 1680
 aattattttt cactctaagt catgtatgtt tctctttgat tatttgcag ttatgtttta
 50 1740
 taagctacta gcaaaataaa acatagcaaa tgaaaaaaaa aaaaaaaaaa aaaaaaaaaa
 1800
 55 aaaa
 1804

5 <210> 14
 <211> 4827
 <212> DNA
 10 <213> Homo sapiens

<400> 14
 15 gcggtggcgc tgcggagacc cgggccagac gcctggcggc cgccggcaca caaggcgctt 60
 tctagctccc tccccgagc gcacagcccg cctccttcg cggcgcctgc agtggcaggc
 120
 20 ttgctctgcc ctaccgtgac gcgctccgga gacgctctgc gggctctgga caccgggtcc
 180
 gcggcggtggg gacgacagac ggaggcgaac gccatcggta gccggtccgc gagccatcgt
 25 240
 tcggggcgca gtcctctccc cggctggccc tcctttctcc ggggcattcg ccaccgcttc
 300
 30 cctgggtga gacgaccggt tcgtcgctc cttgccgtg accgtcgcta gaactcagtt
 360
 gtgcgttgcg gccagtcgcc actgctgagt ggaagcaaaa tgtcagtcag tgtgcatgag
 420
 35 aaccgcaagt ccagggccag cagcggctcc attaacatct atctgtttca caagtcctcc
 480
 tacgctgaca gcgtcctcac tcacctgaat cttttacgcc agcagcgtct cttcactgac
 540
 40 gtccttctcc atgccgaaa taggaccttc cttgccacc gggcagtgtt ggctgcatgc
 600
 agtcgctact ttgaggccat gttcagtggt ggcctgaaag agagccagga cagtgaagtc
 45 660
 aactttgaca attccatcca ccagaagtc ttggagctgc tgcttgacta tgcgtactcc
 720
 50 tcccggtca tcatcaatga agaaaatgca gaatcgctcc tggaagctgg tgacatgctg
 780
 gagtttcaag acatccggga tgcattgtga gatttcctgg aaaagaacct gcatcccacc
 840
 55

aactgcctgg gcatgctgct gctgtctgat gcacaccagt gcaccaagct gtacgaacta
900

5 tcttggagaa tgtgtctcag caacttccaa accatcagga agaataaga tttcctccag
960

ctgccccagg acatggtagt gcaactcttg tccagtgaag agctggagac agaggatgaa
1020

10 aggccttggt acgagtctgc aattaactgg atcagctatg acctgaagaa gcgctattgc
1080

tacctcccag aactgttgca gacagtaagg ctggcacttc tgccagccat ctatctcatg
15 1140

gagaatgtgg ccatggagga actcatcacc aagcagagaa agagtaagga aattgtggaa
1200

20 gaggccatca ggtgcaaact gaaaatcctg cagaatgacg gtgtggtaac cagcctctgt
1260

gcccgcctc ggaaaactgg ccatgccctc ttccttctgg gaggacagac tttcatgtgt
1320

25 gacaagttgt atctggtaga ccagaaggcc aaagaaatca ttccaaggc tgacattccc
1380

agcccaagaa aagagtttag tgcatgtgcg attggctgca aagtgtacat tactgggggg
1440

30 cgggggtctg aaaatggggt ctcgaaagat gtctggggtt atgataccct gcacgaggag
1500

35 tggccaagg ctgccccat gctggtggcc aggtttggcc atggctctgc tgaactgaag
1560

cactgcctgt atgtggttgg ggggcacacg gccgcaactg gctgcctccc ggctccccc
1620

40 tcagtctctc taaagcaggt agaacattat gacccacaa tcaacaaatg gaccatggtg
1680

gccccactcc gagaaggcgt tagcaacgcc gcagtagtga gtgccaaact taagttattt
1740

45 gctttcggag gtaccagtgt cagtcatgac aagctcccca aagttcagtg ttacgatcag
1800

tgtgaaaaca ggtggactgt accggccacc tgtccccagc cctggcggtta cacagcagca
50 1860

gctgtgctgg ggaaccagat ttttattatg gggggtgata cagaattctc tgctgtctct
1920

55 gcttataaat tcaacagtga gacttaccag tggaccaaag tgggagatgt gacagcaaag
1980

cgcatgagct gccatgctgt ggcctctgga aacaaactct acgtggttgg aggatacttt
2040

5 ggcattcagc gatgcaagac tttggactgc tacgatccaa cattagacgt gtggaacagc
2100

atcaccactg tcccgtactc gctgattcct actgcatttg tcagcacctg gaaacatctg
2160

10 ccttcttaaa tgcagtacat tctaaagaga gtgagcatga gctcactcca tcaactcgatg
2220

agataaatatg agattttctac ttcggagagg ccaagtctaa tgaagagaaa aaaaggaaaa
15 2280

gaagttgcaa gactcgaata aaatctgctg caccttgtaa atgctctaac tggacatgaa
2340

20 ggaaaggggc gagggagggg ggtgggattt ttggtgcaag tagcacatgg tttaaataatg
2400

aatgaacaaa cctgtgatct agtccttgtc ttgtaattgt ggattaatgt caatgttaat
2460

25 cagcccctca aaggagaga aaagctggac cttttccctt gctgtaccat attcagcatt
2520

tgatttccat gggccccacc atttatgtgt agaatttgaa atggttgtca cctctctctg
30 2580

aggacagagc ttgaagcctc cacaccagct gctgctggag attcaaagcc caactgtggg
2640

35 tccgagaggg aagctggctg ggctggctga agaataaga ccaactggact ctccgttaat
2700

ctctaagggg tctgctcccc aggaacgttt ctgaacaatg gggactttgt tggtagccat
2760

40 ttggtagatg ttcttttcta tttataagtg actttaaact ttcccttggc tgtaagaag
2820

tttgttatag atttagctat ttattgttcg atgcctgcat gctgaaacaa tgcctacagc
2880

45 tgtcttcaca tgtatggacg tgtgtgaatg gttgtacgtt ttgcacattt tgtggctggt
2940

gagatgtgct ttgctgcaca aacatgaaaa tttttgagtt acaatttggg gcataactgg
50 3000

aggggtgggct ggggaggggt ggatttttaa aatgtcaaga cagggaagga tgacaaaatg
3060

55 gaaatttaaa tgacatccta gaggtagaga aaccgtggag atcgcttttc tcagactcac
3120

caacttttaa tgggatttca tggggtttgg ttgtgctgat agggtaaggg gaggctgctt
 3180
 5 tctgcccttc tccccactcc catctgattt acttaattca gtctcagctg ctgaaatttg
 3240
 gaaaggacca aattgcttta cagttttttt ctttgtgtag tatcttgaaa tcctggaaaa
 3300
 10 ttctatggaa tagttctgta tatagggcac aagtaaaggc attgtccaaa gtttatttat
 3360
 ttatttatta ccctaagaat gctttgccat aaccacattt aatgggaaaa acggcatgta
 15 3420
 tcacagatgt aaattaactc accagattta ctgggcctga actcattctc ttcttgctat
 3480
 20 atgatttagc aagttctaga aggtctccaa gacaataatt acattggcac aatgtatact
 3540
 tcagtgtcga cccgtagcaa atctcttttt aaaaaactct ttggtgcaca agtaacacat
 3600
 25 ttggccacaa aacaccaaag aattgtaggc agtggcccct attgagaagt tttccggtag
 3660
 agttggaaat cagttgtgaa tacattcttt gctagttgga gtgcttggtt actaagcatg
 3720
 30 tgccgtcgta ggtattagtg ctagtctcaa ataggtgctt cccctgaggt gcaggggaag
 3780
 accaaagttt gcaactcgaa ctgctttcgt ccatgtttct cacattgctg tatttttagaa
 3840
 aatagggggt aagactgata acaacctttt acattgtgac tgtgtttgca ttgtctaattg
 3900
 40 acagataaat ccttaacatt tctctccacc ttagtacttt agactaattg tgtttgtccg
 3960
 tccatgccat gaatgagtgg gctgtagttg ggcctaaata aatgagctgt tggaagaaaa
 4020
 45 gaatcacagt actttccagc agtcagtcct tggttcctag atgtgttcta agcaatgcaa
 4080
 atgtctaatt gtccccagt gggcatagtc agtgtcggtt atattgtagc agttacagct
 50 4140
 ctgtagttta tgatgcaaat ctgccaagag agatgtatgt gtcactgcat ggcttctgaa
 4200
 55 agcaggatga attttctgca gctgtttcaa agttggggtc tgttcttgaa tcctctatta
 4260

attactgtgt gtgagccaga gggagctgtg gtaagggttg ggcccccagc ctgtagggaa
 4320
 5 ctttctggac tcccactcct tgaatcgata taggcatttg gtctcactac ttgaccattc
 4380
 tcaccctgtg aaacgtccca cactttgaag caaatacaat tcacagcaca gtacacacaa
 4440
 10 aaaccttggc ataagacaga gaaggttctt cttattttgt gggctgggtg ctgtagaaac
 4500
 atataacaaa gggcagccct ccacttctgg tataattgtg tagccccctt tctttgggct
 15 4560
 tgacacctgt cttgaataag agtgattaga gctgcataat gtccctctct tggctattga
 4620
 20 ccatgtggtt cacgtacaaa actctgtata agttgaagga aaatgttcat gttcatatgt
 4680
 acttgtttgc tatgactaca ttttgagggt ttgtaaaact gttatttttt tttttttcac
 4740
 25 aatgtgaaac tgaaggtaa taaattatta gagattttct cttcaaaaaa aaaaaaaaaa
 4800
 aaaaaaaaaa aaaaaaaaaa aaaaaaa
 30 4827
 <210> 15
 35 <211> 1098
 <212> DNA
 40 <213> Homo sapiens
 <400> 15
 45 cggcacgagg gtcccgcgcg ctctccgac ccgctccgct ccgctccgct cggccccgcg 60
 ccgcccgtca acatgatccg ctgcggcctg gcctgcgagc gctgccgctg gatcctgccc
 120
 50 ctgctcctac tcagcgccat cgccttcgac atcatcgcg cggccggccg cggctgggtg
 180
 cagtctagcg accacggcca gacgtcctcg ctgtgggtga aatgctccca agagggcggc
 240
 55

ggcagcgggt cctacgagga gggctgtcag agcctcatgg agtacgcgtg gggtagagca
300

5 ggggctgcca tgctcttctg tggcttcac ctcctggtga tctgtttcat cctctccttc
360

ttcgccctct gtggacccca gatgcttgct ttcctgagag tgattggagg tctccttgcc
420

10 ttggctgctg tgttcagat catctccctg gtaatttacc ccgtgaagta caccagacc
480

ttcacccttc atgccaaccc tgctgtcact tacatctata actgggccta cggttttggg
540

15 tgggcagcca cgattatcct gattggctgt gcctttctct tctgtgcct cctcaactac
600

20 gaagatgacc ttctgggcaa tgccaagccc aggtacttct acacatctgc ctaacttggg
660

aatgaatgtg ggagaaaatc gctgctgctg agatggactc cagaagaaga aactgtttct
720

25 ccaggcgact ttgaacccat tttttggcag tgttcattat attaaactag tcaaaaatgc
780

taaaataatt tgggagaaaa ttttttttaa gtagtggtat agtttcatgt ttatctttta
840

30 ttatgttttg tgaagttgtg tcttttctact aattacctat actatgcca tatttcctta
900

35 tatctatcca taacatttat actacatttg taagagaata tgcacgtgaa acttaacact
960

ttataaggta aaaatgaggt ttccaagatt taataatctg atcaagttct tgttatttcc
1020

40 aaatagaatg gactcggtct gttaagggtc aaggagaaga ggaagataag gttaaaagtt
1080

gttaatgacc aaacattc
1098

45

<210> 16

50 <211> 1381

<212> DNA

<213> Homo sapiens

55

<400> 16

5 atgcgcgatc tcccggagca tgcgcagcag cggcgccgac gcggggcggt gcctggtgac 60
 cgcgcgcgct cccggaagtg tgccggcgtc gcgcgaaggt tcagcagga gccgtgggcc
 120
 10 gggcgcgcggt ttcccggcac gtgtctcggc acgtggcagc gcgcctggcc ctgggcttgg
 180
 aggcgcgggc gccctggatc cgccggccgt ggtcgccgag tcggtgtcgt ccttgaccat
 240
 15 cgccgacgcg ttcatctgag ccggcgagag ctgagctccg accccgccgc gccccgcgt
 300
 tcccaggagg ttcatctgct ccttccctga ctgcagcgcc aattacagca aagcctggaa
 360
 20 gcttgacgcg cacctgtgca agcacacggg ggagagacca tttgtttgtg actatgaagg
 420
 gtgtggcaag gccttcatca gggactacca tctgagccgc cacattctga ctcacacagg
 25 480
 agaaaagccg tttgtttgtg cagccaatgg ctgtgatcaa aaattcaaca caaatcaaa
 540
 30 cttgaagaaa cattttgaac gcaaacatga aaatcaacaa aaacaatata tatgcagttt
 600
 tgaagactgt aagaagacct ttaagaaaca tcagcagctg aaaatccatc agtgccagaa
 660
 35 taccaatgaa cctctattca agtgtacca ggaaggatgt gggaaacact ttgcatcacc
 720
 cagcaagctg aaacgacatg ccaaggccca cgagggtat gtatgtcaaa aaggatgttc
 780
 40 ctttgtggca aaaacatgga cggaacttct gaaacatgtg agagaaacc ataaagagga
 840
 aatactatgt gaagtatgcc ggaaaacatt taaacgcaa gattacctta agcaacacat
 45 900
 gaaaactcat gcccagaaa gggatgtatg tcgctgtcca agagaaggct gtggaagaac
 960
 50 ctatacaact gtgtttaatc tccaaagcca tatcctctcc ttccatgagg aaagccgcc
 1020
 ttttgtgtgt gaacatgctg gctgtggcaa aacatttgca atgaaacaaa gtctcactag
 1080
 55

gcacgtctgtt gtacatgatc ctgacaagaa gaaaatgaag ctcaaagtca aaaaatctcg
1140

5 tgaaaaacgg gagtttggcc tctcatctca gtggatatat cctcccaaaa gaaacaagg
1200

gcaaggctta tctttgtgtc aaaacggaga gtcaccaac tgtgtggaag acaagatgct
1260

10 ctcgacagtt gcagtactta cccttggtta agaactgcac tgctttgttt aaaggactgc
1320

agaccaagga gtcgagcttt ctctcagagc atgcttttct ttattaaaat tactgatgca
1380

15 g
1381

20

<210> 17

<211> 1978

25 <212> DNA

<213> Homo sapiens

30

<400> 17

gggagggtac ttagggccgg ggctggccca ggctacggcg gctgcagggc tccggcaacc 60

35 gctccggcaa cgccaaccgc tccgtgcgc gcaggctggg ctgcaggctc tcggctgcag
120

cgctgggtgg atctaggatc cggcttccaa catgtggcag ctctgggcct ccctctgctg
180

40 cctgctggtg ttggccaatg cccggagcag gccctcttcc catccctgt cggtatgagct
240

ggtcaactat gtcaacaaac ggaataccac gtggcaggcc gggcacaact tctacaacgt
300

45 ggacatgagc tacttgaaga ggctatgtgg taccttctctg ggtgggcccc agccaccccc
360

gagagttatg tttaccgagg acctgaagct gcctgcaagc ttcatgacac ggaacaatg
420

gccacagtgt cccaccatca aagagatcag agaccagggc tcctgtggct cctgctgggc
480

55

cttcggggct gtggaagcca tctctgaccg gatctgcatc cacaccaatg cgcacgtcag
 540
 5 cgtggagggtg tcggcggagg acctgctcac atgctgtggc agcatgtgtg gggacggctg
 600
 taatggtggc tatcctgctg aagcttggaa cttctggaca agaaaaggcc tggtttctgg
 660
 10 tggcctctat gaatcccatg tagggtgcag accgtactcc atccctccct gtgagcacca
 720
 cgtcaacggc tcccgggccc catgcacggg ggaggagat accccaagt gtagcaagat
 15 780
 ctgtgagcct ggctacagcc cgacctacaa acaggacaag cactacggat acaattccta
 840
 20 cagcgtctcc aatagcgaga aggacatcat ggccgagatc tacaaaaacg gcccctgga
 900
 gggagctttc tctgtgtatt cggacttcct gctctacaag tcaggagtgt accaacacgt
 960
 25 caccggagag atgatgggtg gccatgcat ccgcctcctg ggctggggag tggagaatgg
 1020
 cacaccctac tggctggttg ccaactcctg gaacactgac tggggtgaca atggcttctt
 1080
 30 taaaatactc agaggacagg atcactgtgg aatcgaatca gaagtgggtg ctggaattcc
 1140
 35 acgcaccgat cagtactggg aaaagatcta atctgccgtg ggctgtcgt gccagtcctg
 1200
 ggggcgagat cggggtagaa atgcatttta ttctttaagt tcacgtaaga tacaagtttc
 1260
 40 agacagggtc tgaaggactg gattggccaa acatcagacc tgtcttccaa ggagaccaag
 1320
 tcctggctac atcccagcct gtggttacag tgcagacagg ccatgtgagc caccgctgcc
 1380
 45 agcacagagc gtccttcccc ctgtagacta gtgccgtagg gagtacctgc tgccccagct
 1440
 gactgtggcc ccctccgtga tccatccatc tccaggagc aagacagaga cgcaggaatg
 50 1500
 gaaagcggag ttcctaacag gatgaaagtt ccccatcag ttccccagt acctccaagc
 1560
 55 aagtagcttt ccacatttgt cacagaaatc agaggagaga tgggtgtggg agcccttttg
 1620

agaacgccag tctcccaggc cccctgcac tatcgagttt gcaatgtcac aacctctctg
 1680
 5 atcttgtgct cagcatgatt ctttaataga agttttatatt tttcgtgcac tctgctaatac
 1740
 atgtgggtga gccagtggaa cagcgggaga cctgtgctag ttttacagat tgcctcctaa
 1800
 10 tgacgcggct caaaaggaaa ccaagtggc aggagttgtt tctgaccac tgatctctac
 1860
 taccacaagg aaaatagttt aggagaaacc agcttttact gtttttgaaa aattacagct
 15 1920
 tcaccctgtc aagttaacaa ggaatgcctg tgccaataaa agttttctcc aacttgaa
 1978
 20
 <210> 18
 <211> 1074
 25 <212> DNA
 <213> Homo sapiens
 30
 <400> 18
 ggtcaggaaa gctcaggcaa gccaccctc aggcatata gctagactcc gagcttactg 60
 35 ggcagtcac tgattcgacc aacatcagtt cgcagggtt aagcccagtc ccttacggcg
 120
 gctggggagg gaccaggccc aagtatataa agctccctga gggtcgcgt tggctttgcg
 40 180
 cctgtgagtg tgattcaaga acgtccagc gcccttggct cctttcggag tgtgacccg
 240
 tgcttgacg ggacacgtta cccagctcgg gtgagaaggg tatcttcgg gaacctcgcc
 45 300
 tttaatagca caacgagcgc agagtccact ggatctgcga gaagaaaccg cgctaactag
 360
 50 tttgtcccta cggccgcctc gtagtcactg ccgcggcgcc ttgagtctcc gggccgcctt
 420
 gccatggctg ccggtggtgt catcgctcca gttggcgaga gtttgcgcta cgctgagtac
 480
 55

ttgcagccct cggccaaacg gccagacgcc gacgtcgacc agcagggact ggtaagaagt
 540
 5 ttgatagctg taggactggg tgttcagct cttgcatttg caggtcgcta cgcatttcgg
 600
 atctggaaac ctctagaaca agttatcaca gaaactgcaa agaagatttc aactcctagc
 660
 10 ttttcatcct actataaagg aggatttgaa cagaaaatga gtaggcgaga agctgggtctt
 720
 attttaggtg taagcccatc tgctggcaag gctaagatta gaacagctca taggagagtc
 15 780
 atgattttga atcaccacaga taaagggtga tctccttacg tagcagccaa aataaatgaa
 840
 20 gcaaaaagact tgctagaaac aaccaccaa cattgatgct taaggaccac actgaaggaa
 900
 aaaaaaagag gggacttoga aaaaaaaaa agccctgcaa aatattctaa aacatgggtct
 960
 25 tcttaatttt ctatatgat tgaccacagt cttatcttcc accattaagc tgtataacaa
 1020
 taaatgtta atagtcttg tttttattat cttttaaaga tctccttaaa ttct
 30 1074

 <210> 19
 35 <211> 4098
 <212> DNA
 40 <213> Homo sapiens

 <400> 19
 45 ggtggcctct gtggccgtcc aggctagcgg cggcccgag gcggcgggga gaaagactct 60
 ctcacctggt cttgcggctg tggccaccgc cggccagggg tgtggagggc gtgctgccgg
 120
 50 agacgtccgc cgggctctgc agttccgccg ggggtcgggc agctatggag ccgcggccca
 180
 cggcgcctc ctccggcgcc ccgggactgg ccggggtcgg ggagacgccg tcagccgctg
 240
 55

cgctggccgc agccaggggtg gaactgcccg gcacggctgt gccctcggtg ccggaggatg
 300
 5 ctgcgcccgc gagccgggac ggcggcgggg tccgcgatga gggccccgcg gcggccgggg
 360
 acgggctggg cagacccttg gggcccaccc cgagccagag ccgtttccag gtggacctgg
 420
 10 tttccgagaa cgccgggcgg gccgctgctg cggcggcggc ggcggcggcg gcagcggcgg
 480
 cggctggtgc tggggcgggg gccaaagcaga cccccgcgga cggggaagcc agcggcgaga
 540
 15 gcgagccagc taaaggcagc gaggaagcca agggccgctt ccgctgaac ttcgtggacc
 600
 20 cagctgcctc ctgctcggct gaagacagcc tgtcagatgc tgccggggtc ggagtcgacg
 660
 ggcccaacgt gagcttcag aacggcgggg acacggtgct gagcgagggc agcagcctgc
 720
 25 actccggcgg cggcggcggc agtgggcacc accagcacta ctattatgat acccacacca
 780
 acacctaacta cctgcgcacc ttcggccaca acaccatgga cgctgtgccc aggatcgatc
 840
 30 actaccggca cacagccgcg cagctgggcg agaagctgct ccggcctagc ctggcggagc
 900
 35 tccacgacga gctggaaaag gaacctttt aggatggctt tgcaaattgg gaagaaagta
 960
 ctccaaccag agatgctgtg gtcacgtata ctgcagaaag taaaggagtc gtgaagtttg
 1020
 40 gctggatcaa ggggtgatta gtacgttgta tgttaaacad ttggggtgtg atgcttttca
 1080
 ttagattgtc atggattgtg ggtcaagctg gaataggtct atcagtcctt gtaataatga
 1140
 45 tggccactgt tgtgacaact atcacaggat tgtctacttc agcaatagca actaatggat
 1200
 ttgtaagagg aggaggagca tattatttaa tatctagaag tctagggcca gaatttggtg
 1260
 50 gtgcaattgg tctaactctc gcctttgcc aacgtgttgc agttgctatg tatgtggttg
 1320
 55 gatttgcaga aaccgtggtg gagttgctta aggaacattc catacttatg atagatgaaa
 1380

tcaatgatat ccgaattatt ggagccatta cagtcgtgat tcttttaggt atctcagtag
1440

5 ctggaatgga gtgggaagca aaagctcaga ttgttctttt ggtgaccta cttcttgcta
1500

ttggtgattt cgtcatagga acatttatcc cactggagag caagaagcca aaagggtttt
1560

10 ttggttataa atctgaaata tttaatgaga actttgggcc cgattttcga gaggaagaga
1620

ctttcttttc tgtatttgcc atcttttttc ctgctgcaac tggatttctg gctggagcaa
15 1680

atatctcagg tgatcttgca gatcctcagt cagccatacc caaaggaaca ctctagcca
1740

20 ttttaattac tacattgggt tacgtaggaa ttgcagtatc tgtaggttct tgtgttggtc
1800

gagatgccac tggaaacgtt aatgacacta tcgtaacaga gctaacaac tgtacttctg
1860

25 cagcctgcaa attaaacttt gatttttcat cttgtgaaag cagtccttgt tctatggcc
1920

taatgaacaa cttccaggta atgagtatgg tgtcaggatt tacaccacta atttctgcag
30 1980

gtatattttc agccactctt tcttcagcat tagcatccct agtgagtgct cccaaaatat
2040

35 ttcaggctct atgtaaggac aacatctacc cagctttcca gatgtttgct aaagggtatg
2100

ggaaaaataa tgaacctctt cgtggctaca tcttaacatt ctttaattgca cttggattca
2160

40 tcttaattgc tgaactgaat gttattgcac caattatctc aaacttcttc cttgcatcat
2220

atgcattgat caatttttca gtattccatg catcacttgc aaaatctcca ggatggcgctc
2280

45 ctgcattcaa atactacaac atgtggatat cacttcttgg agcaattctt tgttgcatag
2340

taatgttcgt cattaactgg tgggctgcat tgctaacata tgtgatagtc cttgggctgt
50 2400

atatttatgt tacctacaaa aaaccagatg tgaattgggg atcctctaca caagccctga
2460

55 cttacctgaa tgcactgcag cattcaattc gtctttctgg agtggaagac cacgtgaaaa
2520

acttttaggcc acagtgtctt gttatgacag gtgctccaaa ctcacgtcca gctttacttc
 2580
 5 atcttgttca tgatttcaca aaaaatgttg gtttgatgat ctgtggccat gtacatatgg
 2640
 gtcctcgaag acaagccatg aaagagatgt ccatcgatca agccaaatat cagcgatggc
 2700
 10 ttattaagaa caaaatgaag gcattttatg ctccagtaca tgcagatgac ttgagagaag
 2760
 gtgcacagta tttgatgcag gctgctggtc ttggtcgtat gaagccaaac aactttgtcc
 15 2820
 ttggatttaa gaaagattgg ttgcaagcag atatgagggg tgtggatatg tatataaact
 2880
 20 tatttcatga tgcttttgac atacaatatg gagtagtggt tattcgcta aaagaaggtc
 2940
 tggatatatc tcatcttcaa ggacaagaag aattattgtc atcacaagag aaatctcctg
 3000
 25 gcaccaagga tgtggtagta agtgtggaat atagtaaaaa gtccgattta gatacttcca
 3060
 aaccactcag tgaaaaacca attacacaca aagttgagga agaggatggc aagactgcaa
 3120
 30 ctcaaccact gttgaaaaaa gaatccaaag gccctattgt gcctttaaat gtagctgacc
 3180
 aaaagcttct tgaagctagt acacagtttc agaaaaaaca aggaaagaat actattgatg
 35 3240
 tctgggtggct ttttgatgat ggaggtttga ccttattgat accttacctt ctgacgacca
 3300
 40 agaaaaaatg gaaagactgt aagatcagag tattcattgg tggaaagata aacagaatag
 3360
 accatgaccg gagagcgatg gctactttgc ttagcaagtt ccg gatagac ttttctgata
 3420
 45 tcatggttct aggagatata aataccaaac caaagaaaga aaatattata gcttttgagg
 3480
 aaatcattga gccatacaga cttcatgaag atgataaaga gcaagatatt gcagataaaa
 50 3540
 tgaaagaaga tgaaccatgg cgaataacag ataatgagct tgaactttat aagaccaaga
 3600
 55 cataccggca gatcagggtta aatgagttat taaaggaaca ttcaagcaca gctaataatta
 3660

ttgtcatgag tctcccagtt gcacgaaaag gtgctgtgtc tagtgctctc tacatggcat
 3720
 5 ggtagaagc tctatctaag gacctaccac caatcctcct agttcgtggg aatcatcaga
 3780
 gtgtccttac cttctattca taaatgttct atacagtgga cagccctcca gaatgggtact
 3840
 10 tcagtgccta gtgtagtaac ctgaaatctt caatgacaca ttaacatcac aatggcgaat
 3900
 ggtgactttt ctttcacgat ttcattaatt tgaaagcaca caggaaagct tgctccattg
 15 3960
 ataacgtgta tggagacttc ggTTTTtagtc aattccatat ctcaatctta atggtgattc
 4020
 20 ttctctgttg aactgaagtt tgtgagagta gttttccttt gctacttgaa tagcaataaa
 4080
 agcgtgttaa ctttttgg
 4098
 25
 <210> 20
 30 <211> 3120
 <212> DNA
 <213> Homo sapiens
 35
 <400> 20
 40 aaaggaaaca caagttgctt ttgataacac atgatgcaaa gaaagaatta gaaagaatga 60
 gcaatgaagc cggataaat gacaaacaag tgtccaaagg cccaagaagt tactaccaaa
 120
 agctttcaaa caatattggt ttatctttta agacacatcc atagcatact ttaaaaataa
 45 180
 ggaacttgaa caaggagaac cacaagaaaa actaaatctt agaggctgcg aagttgtgcc
 240
 50 cgatgtaa atgtatgtga gaaaatttgg aatcaagtta ctaatccctg ttgccgatgg
 300
 tatgaatgaa atgtatttga gatgtgacca tgagaatcaa tacgcccaat ggatggctgc
 360
 55

ctgcatgttg gcatcgaagg gcaaaacccat ggcagacagc tcctaccagc cagaggtcct
 420

5 caacatcctt tcatttctga ggatgaaaaa caggaactct gcatctcagg tggcttcag
 480

tctcgaaaac atggatatga acccagaatg ttttgtgtca ccacggtgtg caaaaagaca
 540

10 caaatccaaa cagctggccg ccgggatcct ggaggcgac cagaacgtgg ccagatgcc
 600

cctggtcgaa gccaaagtgc ggttcatcca ggcgtggcag tcaactgctg agtttggcct
 15 660

cacctactac cttgtcagat ttaaaggaag caaaaaagat gacattctgg gagtttcata
 720

20 taacagggttg attaaaattg atgcagccac cgggattcca gtgacaacat ggagattcac
 780

aaatatcaaa cagtggaatg taaactggga aaccggcag gtggatcatc agtttgacca
 840

25 aaacgtcttt actgctttca cctgcctgag tgcagattgc aagattgtgc acgagtacat
 900

tggcggctac attttcttgt ccacccgctc caaggaccag aatgaaacac tcgatgagga
 30 960

cttgttccac aaattgaccg gcggtcagga ttgaaacaag cacgcgtgct cggctcacac
 1020

35 caacaaggca agccaaaggc gcccctcccc agagggatcc ctaacgtgcc cagcatgtag
 1080

attctggact aacagacaac atacattcac cgctggtcac ccagatcctc attcaaacc
 1140

40 actgctggca catccctttc cttactttgc cctgtgctac cagccacgga aggagcctct
 1200

cttgtttttt ctataaaatg ggtaggcagg agaaaagcag gtgccctaag attgctctaa
 1260

45 ggcccagcat gtggttacag ttctctgact tgcagaacct gccagggtga tggctacaag
 1320

ttatcctcgt gctgatctgt ctcatctact agtcaatgga gaagacagaa aggtaaaaat
 50 1380

cacgtgtagc aagaacaact cttatttcac aaactcaggt atgaaacgaa acgcctgtcc
 1440

55 ttcattggaac tgcttttagc tcctgtcttt tcaaaatggc agagggagtt cctacacaca
 1500

ctttttccct ggaggccaag gtctaggggt agaaagggga ggggtggggc taccaggtag
 1560
 5 cagttgacaa cccaaggtca gaggagtggc cctcagtgtc atctgtccac agtgatacct
 1620
 gccaagatga ccactgaccc acatctgggc ttagtcattg gtctcctcag atttctgggg
 1680
 10 ccacctgcaa gccccattcc attcctacag atctctcagc cacctgtaag tcctttgtga
 1740
 agatgtgggt gacacagggg gacaggaaaa ccattttctc aaccagatc catgtctcca
 1800
 15 ctgcttctac tctgggttgg gattcaggaa gacaggcaca gtcctctctg ttcatagaaa
 1860
 20 cacctgccag tgtcaaggat tccagtcagg tgtctatccc aactggtcag ggagagaagg
 1920
 gcagacccat tctcaaagac caccatgttc aaggctctgac agctccccac tggctgcccc
 1980
 25 cacaggggct ttaggctggg ctgggtcatg gggaagcgtc cctcttatcg ctggctctgtg
 2040
 ttctcctgga tttggatatc atgttggtac gactcctggc cttttatcta aaggactttg
 2100
 30 gcttttgtaa atcacaagcc aataatagac tttttctccc ccctctgttt tttgctgtgt
 2160
 catctctgcc ttgagactgc cttgagacag tgcttgccct gagagagtga gccaatatc
 2220
 35 agctgcctga attgtcattt tccattttgg tttgttagag gtgggagggg tgggttttga
 2280
 40 gaaggtcaaa agcaatacca gaagtaaagg gaaatatcag acaatatattt attatttttt
 2340
 catagatggt ctgccacaca aagaacttgg ggtgtaagga taaggcaaaa gctccaatcc
 2400
 45 catttttcag ttctcctagg atgcaccctc caggagacct ggccagagtt ccgaggcccc
 2460
 tgagcgtcag ctgttgcttt attttccatc aaagccctct gagaagtga acctcagcaa
 2520
 50 ttccgggagc cacatagaga cagacttggc aagggacccc ctggttctga gccagtagct
 2580
 gccatctgga aattcctctt ttagcctctc cttagaggtg aatgtgaatg aagcctccca
 2640

ggcaccgcgt gaatttctga ggccttgctt aaagctcaga agtggtttag gcatttgaa
2700

5 aatctggttc acatcataaa gaacttgatt tgaaatgttt tctatagaaa caagtgctaa
2760

gtgtaccgta ttatacttga tgttggtcat ttctcagtc ttttctcag ttctattatt
2820

10 ttagaaccta gtcagttctt taagattata actgggtccta cattaaaata atgcttctcg
2880

atgtcagatt ttacctgttt gctgctgaga acatctctgc ctaatttacc aaagccagac
2940

15 cttcagttca acatgcttcc ttagcttttc atagttgtct gacatttcca tgaaaacaaa
3000

20 ggaaccaact ttgttttaac caaactttgt ttggttacag ttttcagggg agcgtttctt
3060

ccatgacaca cagcaacatc ccaaagaaat aaacaagtgt gacaaaaaaaa aaaaaaaaaa
3120

25

30 <210> 21
<211> 1337
<212> DNA

35 <213> Homo sapiens

40 <400> 21

ctggcgctcc ctttccggcc ggtcccatg gaggcgctgg ggaagctgaa gcagttcgat 60

gcctacccca agactttgga ggacttcggg gtcaagacct gcggggggcgc caccgtgacc
120

45 attgtcagtg gccttctcat gctgctaactg ttcctgtccg agctgcagta ttacctcacc
180

acggaggtgc atcctgagct ctacgtggac aagtcgcggg gagataaact gaagatcaac
240

50 atcgatgtac tttttccgca catgccttgt gcctatctga gtattgatgc catggatgtg
300

55 gccggagaac agcagctgga tgtggaacac aacctgttca agcaacgact agataaagat
360

ggcatccccg tgagctcaga ggctgagcgg catgagcttg ggaaagtcga ggtgacggtg
 420
 5 tttgaccctg actccctgga ccctgatcgc tgtgagagct gctatggtgc tgaggcagaa
 480
 gatatcaagt gctgtaacac ctgtgaagat gtgcgggagg catatcgccg tagaggctgg
 540
 10 gccttcaaga acccagatac tattgagcag tgccggcgag agggcttcag ccagaagatg
 600
 caggagcaga agaatgaagg ctgccagggtg tatggcttct tggaagtcaa taagggtggc
 15 660
 ggaaacttcc actttgcccc tgggaagagc ttccagcagt cccatgtgca cgtccatgac
 720
 20 ttgcagagct ttggccttga caacatcaac atgaccact acatccagca cctgtcattt
 780
 ggggaggact atccaggcat tgtgaacccc ctggaccaca ccaatgtcac tgcgcccaa
 840
 25 gcctccatga tgttcagta ctttgtgaag gtggtgccca ctgtgtacat gaagggtggac
 900
 ggagaggtac tgaggacaaa tcagttctct gtgaccagac atgagaaggt tgccaatggg
 960
 30 ctgttgggcg accaaggcct tcccggagtc ttctctctct atgagctctc gcccatgatg
 1020
 gtgaagctga cggagaagca caggtccttc acccacttcc tgacaggtgt gtgcgccatc
 35 1080
 attgggggca tgttcacagt ggctggactc atcgattcgc tcatctacca ctcagcacga
 1140
 40 gccatccaga agaaaattga tctaggaag acaacgtagt caccctcggg gcttcctctg
 1200
 tctctctttt ctccctggcc tgtggttgtc cccagcctc tgccaccctc cacctcctcg
 1260
 45 gtcagcccca gcccaggtt gataaatcta ttgattgatt gtgatagtaa aaaaaaaaaa
 1320
 aaaaaaaaaa aaaaaaa
 50 1337

 <210> 22
 55 <211> 2908

<212> DNA

<213> Homo sapiens

5

<400> 22

10 ctgctcgcgg cgccgcctcc tgctcctccc gctgctgctg ccgctgccgc cctgagtcac 60
 tgcctgcgca gctccggccg cctggctccc catactagtc gccgatattt ggagttctta
 120
 15 caacatggca gacattgaca acaaagaaca gtctgaactt gatcaagatt tggatgatgt
 180
 tgaagaagta gaagaagagg aaactggtga agaaacaaaa ctcaaagcac gtcagctaac
 240
 20 tgttcagatg atgcaaaatc ctgagattct tgcagccctt caagaaagac ttgatggtct
 300
 ggtagaaaca ccaacaggat acattgaaag cctgcctagg gtagttaaaa gacgagtga
 360
 25 tgctctcaaa aacctgcaag ttaaatgtgc acagatagaa gccaaattct atgaggaagt
 420
 30 tcacgatctt gaaaggaagt atgctgttct ctatcagcct ctatttgata agcgatttga
 480
 aattattaat gcaatttatg aacctacgga agaagaatgt gaatggaaac cagatgaaga
 540
 35 agatgagatt tcggaggaat tgaaagaaaa ggccaagatt gaagatgaga aaaaggatga
 600
 agaaaaagaa gaccccaaag gaattcctga attttggtta actgttttta agaatgttga
 660
 40 cttgctcagt gatatggttc aggaacacga tgaacctatt ctgaagcact tgaaagatat
 720
 taaagtgaag ttctcagatg ctggccagcc tatgagtttt gtcttagaat ttcactttga
 780
 45 acccaatgaa tattttacaa atgaagtgtc gacaaagaca tacaggatga ggtcagaacc
 840
 50 agatgattct gatccctttt cttttgatgg accagaaatt atgggttgta cagggtgcc
 900
 gatagattgg aaaaaaggaa agaatgtcac tttgaaaact attaagaaga agcagaaaca
 960
 55

caagggacgt gggacagttc gtactgtgac taaaacagtt tccaatgact ctttcttta
 1020
 5 cttttttgcc cctcctgaag ttcctgagag tggagatctg gatgatgatg ctgaagctat
 1080
 ccttgctgca gacttcgaaa ttggtcactt ttacgtgag cgtataatcc caagatcagt
 1140
 10 gttatatattt actggagaag ctattgaaga tgatgatgat gattatgatg aagaaggatga
 1200
 agaagcggat gaggaagggg aagaagaagg agatgaggaa aatgatccag actatgaccc
 1260
 15 aaagaaggat caaaacccag cagagtgcaa gcagcagtga agcaggatgt atgtggcctt
 1320
 20 gaggataacc tgcactgggc taccttctgc ttccctggaa aggatgaatt tacatcattt
 1380
 gacaagccta ttttcaagtt atttgttggt tgtttgcttg tttttgtttt tgcagctaaa
 1440
 25 ataaaaattt caaatacaat tttagttctt acaagataat gtcttaattt tgtaccaatt
 1500
 caggtagaag tagaggccta ccttgaatta agggttatac tcagttttta acacattgtt
 1560
 30 gaagaaaagg taccagcttt ggaacgagat gctatactaa taagcaagtg taacaaaaaa
 1620
 35 aaaaaaagag gaagaaaatc ttaagtgatt gatgctgttt tcttttaaaa aaaaaaaaaa
 1680
 aaattcatatt tctttgggtt agagctagag agaaggcccc aagcttctat ggtttcttct
 1740
 40 aattcttatt gcttaaagta tgagtatgtc acttaccgtt gcttctgttt actgtgtaat
 1800
 taaaatgggt agtactgttt acctaactac ctcatggatg tgttaaggca tattgagtta
 1860
 45 aatctcatat aatgtttctc aatcttgta aaagctcaaa attttgggcc tatttgtaat
 1920
 gccagtgtga cactaagcat tttgttcaca ccacgctttg ataactaaac tggaaaacaa
 1980
 50 aggtgttaag tacctctgtt ctggatctgg gcagtcagca ctcttttttag atctttgtgt
 2040
 55 ggctcctatt tttatagaag tggagggatg cactatttca caaggtccaa gatttgtttt
 2100

cagatatttt tgatgactgt attgtaaata ctacagggat agcactatag tattgtagtc
2160

5 atgagactta aagtggaaat aagactattt ttgacaaaag atgccattaa atttcagact
2220

gtagagccac atttacaata cctcaggcta attactgtta attttgggggt tgaacttttt
2280

10 ttgacagtga ggggtggatta ttggattgtc attagaggaa ggtctagatt tctgtctctt
2340

aataaaatta cattgaattg attttttagag gtaatgaaaa cttcctttct gagaagttag
15 2400

tgттаagggtc ttggaatgtg aacacattgt ttgtagtgct atccattcct ctctgagat
2460

20 tttaacttac tactggaaat ccttaaccaa ttataatagc tttttttctt tattttcaaa
2520

atgatttcct ttgctttgat tagacactat gtgctttttt tttttaacca tagttcatcg
2580

25 aaatgcagct ttttctgaac ttcaaagata gaatccatt tttaatgaac tgaagtagca
2640

aaatcatctt tttcattctt taggaaatag ctattgcaa agtgaagggt tagataatac
30 2700

ctagtcttgt tacataaagg ggatgtgggt tgcagaagaa ttttctttat aaaattgaag
2760

35 ttttaaggga cgtcagtgtt tatgccattt ttccagttcc aaaatgattc cattccattc
2820

tagaaatttg aagtatgtaa cctgaaatcc ttaataaaaat ttggatttaa ttttataaaa
2880

40 aaaaaaaaaa aaaaaaaaaa aaaaaaaaa
2908

45 <210> 23

<211> 3213

<212> DNA

50 <213> Homo sapiens

55 <400> 23

agagactcaa gatgattccc tttttaccca tgttttctct actattgctg cttattgtta 60
 accctataaa cgccaacaat cattatgaca agatcttggc tcatagtcgt atcaggggtc
 5 120
 gggaccaagg cccaaatgtc tgtgcccttc aacagatttt gggcaccaaa aagaaatact
 180
 tcagcacttg taagaactgg tataaaaagt ccatctgtgg acagaaaacg actgttttat
 10 240
 atgaatgttg ccttggttat atgagaatgg aaggaatgaa aggctgcca gcagttttgc
 300
 ccattgacca tgtttatggc actctgggca tcgtgggagc caccacaacg cagcgctatt
 15 360
 ctgacgcctc aaaactgagg gaggagatcg agggaaaggg atccttcact tactttgcac
 420
 cgagtaatga ggcttgggac aacttggatt ctgatatccg tagaggtttg gagagcaacg
 480
 tgaatgttga attactgaat gctttacata gtcacatgat taataagaga atgttgacca
 25 540
 aggacttaaa aaatggcatg attattcctt caatgtataa caatttgggg cttttcatta
 600
 accattatcc taatgggggtt gtcactgtta attgtgctcg aatcatccat gggaaccaga
 30 660
 ttgcaacaaa tgggtgttgtc catgtcattg accgtgtgct tacacaaatt ggtacctcaa
 720
 ttcaagactt cattgaagca gaagatgacc tttcatcttt tagagcagct gccatcacat
 35 780
 cggacatatt ggaggccctt ggaagagacg gtcacttcac actctttgct cccaccaatg
 40 840
 aggcttttga gaaacttcca cgagggtgtcc tagaaagggt catgggagac aaagtggctt
 900
 ccgaagctct tatgaagtac cacatcttaa atactctcca gtgttctgag tctattatgg
 45 960
 gaggagcagt ctttgagacg ctggaaggaa atacaattga gataggatgt gacggtgaca
 1020
 gtataacagt aaatggaatc aaaatggtga acaaaaagga tattgtgaca aataatggtg
 50 1080
 tgatccattt gattgatcag gtccctaattc ctgattctgc caaacaagtt attgagctgg
 1140
 55

ctggaaaaca gcaaaccacc ttcacggatc ttgtggccca attaggcttg gcatctgctc
 1200
 5 tgaggccaga tggagaatac actttgctgg cacctgtgaa taatgcattt tctgatgata
 1260
 ctctcagcat ggttcagcgc ctccctaaat taattctgca gaatcacata ttgaaagtaa
 1320
 10 aagttggcct taatgagctt tacaacgggc aaatactgga aaccatcgga ggcaaacagc
 1380
 tcagagtctt cgtatatcgt acagctgtct gcattgaaaa ttcattgatg gagaaaggga
 1440
 15 gtaagcaagg gagaaacggt gcgattcaca tattccgcga gatcatcaag ccagcagaga
 1500
 20 aatccctcca tgaaaagtta aaacaagata agcgcttttag caccttcctc agcctacttg
 1560
 aagctgcaga cttgaaagag ctccctgacac aacctggaga ctggacatta tttgtgccaa
 1620
 25 ccaatgatgc ttttaaggga atgactagtg aagaaaaaga aattctgata cgggacaaaa
 1680
 atgctcttca aaacatcatt ctttatcacc tgacaccagg agttttcatt ggaaaaggat
 1740
 30 ttgaacctgg tggtactaac attttaaaga ccacacaagg aagcaaaatc tttctgaaag
 1800
 aagtaaatga tacacttctg gtgaatgaat tgaaatcaaa agaactctgac atcatgacaa
 1860
 35 caaatggtgt aattcatgtt gtagataaac tcctctatcc agcagacaca cctggttgaa
 1920
 40 atgatcaact gctggaaata cttaataaat taatcaaata catccaaatt aagtttgttc
 1980
 gtggtagcac cttcaaagaa atccccgtga ctgtctatac aactaaaatt ataaccaag
 2040
 45 ttgtggaacc aaaaattaaa gtgattgaag gcagtcttca gcctattatc aaaactgaag
 2100
 gaccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg attaaagaag
 2160
 50 gtgaaacaat aactgaagtg atccatggag agccaattat taaaaaatc accaaaatca
 2220
 55 ttgatggagt gcctgtggaa ataactgaaa aagagacacg agaagaacga atcattacag
 2280

gtcctgaaat aaaatacact aggatttcta ctggaggtgg agaaacagaa gaaactctga
2340

5 agaaattggtt acaagaagag gtcaccaagg tcaccaaatt cattgaaggt ggtgatggtc
2400

at ttatttga agatgaagaa attaaaagac tgcttcaggg agacacaccc gtgaggaagt
2460

10 tgcaagccaa caaaaaagtt caagggttcta gaagacgatt aagggaaggt cgttctcagt
2520

gaaaatccaa aaaccagaaa aaaatgttta tacaacccta agtcaataac ctgaccttag
2580

15 aaaattgtga gagccaagtt gacttcagga actgaaacat cagcaciaag aagcaatcat
2640

caaataattc tgaacacaaa tttaatattt ttttttctga atgagaaaaca tgagggaaat
2700

tg tggagtta gcctcctgtg gtaaaggaat tgaagaaaat ataacacctt acaccctttt
2760

25 tcatcttgac attaaaagtt ctggctaact ttggaatcca ttagagaaaa atccttgtca
2820

ccagattcat tacaattcaa atcgaagagt tgtgaactgt tatccattg aaaagaccga
2880

30 gccttgatg tatgttatgg atacataaaa tgcacgcaag ccattatctc tccatgggaa
2940

gctaagttat aaaaataggt gcttgggtga caaaactttt tatatcaaaa ggctttgcac
3000

35 atttctatat gagtgggttt actggtaaat tatgttattt tttacaacta attttgtact
3060

ctcagaatgt ttgtcatatg cttcttgcaa tgcataattt ttaatctcaa acgtttcaat
3120

aaaaccattt ttcagatata aagagaatta cttcaaattg agtaattcag aaaaactcaa
3180

45 gatttaagtt aaaaagtggg ttggacttgg gaa
3213

50 <210> 24

<211> 10558

<212> DNA

55

<213> Homo sapiens

5

<400> 24

cagtttggag ctcagtcttc caccaaaggc cgttcagttc tcctgggctc cagcctcctg 60

10

caaggactgc aagagttttc ctccgcagct ctgagtctcc acttttttgg tggagaaagg
120ctgcaaaaag aaaaagagac gcagtgagtg ggaaaagtat gcatacctatt caaacctaata
180

15

tgaatcgagg agcccaggga cacacgcctt caggtttgct caggggttca tatttggtgc
240ttagacaaat tcaaatgag gaaacatcgg cacttgccct tagtggccgt cttttgcctc
300

20

tttctctcag gctttcctac aactcatgcc cagcagcagc aagcagatgt caaaaatggt
360

25

gcggctgctg atataatatt tctagtggat tcctcttgga ccattggaga ggaacatttc
420caacttgttc gagagtttct atatgatgtt gtaaaatcct tagctgtggg agaaaatgat
480

30

ttccattttg ctctggtcca gttcaacgga aaccacata ccgagttcct gttaaatacg
540tattcgacta aacaagaagt cttttctcat attccaaca tgtcttatat tgggggaacc
600

35

aatcagactg gaaaaggatt agaatacata atgcaaagcc acctcacaa ggctgctgga
660agccggggccg gtgacggagt ccctcagggt atcgtagtgt taactgatgg aactcgaag
720

40

gatggccttg ctctgccctc agcggaaactt aagtctgctg atgttaacgt gtttgcaatt
780ggagttgagg atgcagatga aggagcggtta aaagaaatag caagtgaacc gctcaatatg
840

45

catatgttca acctagagaa ttttacctca cttcatgaca tagtaggaaa cttagtgtcc
900

50

tgtgtgcatt catccgtgag tccagaaagg gctggggaca cggaaaccct taaagacatc
960acagcacaag actctgctga cattattttc cttattgatg gatcaaaca caccggaagt
1020

55

gtcaatttcg cagtcattct cgacttcctt gtaaattctcc ttgagaaact cccaattgga
1080

5 actcagcaga tccgagtggg ggtgggtccag tttagcgatg agcccagaac catgttttcc
1140

ttggacacct actccaccaa ggcccaggtt ctgggtgcag tgaaagccct cgggtttgct
1200

10 ggtggggagt tggccaatat cggcctcgcc cttgatttcg tgggtggagaa ccacttcacc
1260

cgggcagggg gcagccgcgt ggaggaaggg gttccccagg tgctggtcct cataagtgcc
1320

15 gggccttcta gtgacgagat tcgctacggg gtggtagcac tgaagcaggc tagcgtgttc
1380

tcattcggcc ttggagccca ggccgcctcc agggcagagc ttcagcacat agctaccgat
1440

gacaacttgg tgtttactgt cccggaattc cgtagctttg gggacctcca ggagaaatta
1500

25 ctgccgtaca ttgttggcgt ggcccaaagg cacattgtct tgaaaaccgc aaccattgtc
1560

acacaagtca ttgaagtcaa caagagagac atagtcttcc tgggtgatgg ctcatctgca
1620

30 ctgggactgg ccaacttcaa tgccatccga gacttcattg ctaaagtcac ccagaggctg
1680

gaaatcggac aggatcttat ccagggtggca gtggcccagt atgcagacac tgtgaggcct
1740

gaattttatt tcaataccca tccaacaaaa agggaagtca taaccgctgt gcggaaaatg
1800

40 aagcccctgg acggctcggc cctgtacacg ggctctgctc tagactttgt tcgtaacaac
1860

ctattcacga gttcagccgg ctaccgggct gccgagggga ttcctaagct tttggtgctg
1920

45 atcacagggt gtaagtccct agatgaaatc agccagcctg cccaggagct gaagagaagc
1980

agcataatgg cctttgccat tgggaacaag ggtgccgac aggctgagct ggaagagatc
2040

gctttcgact cctccctggt gttcatccca gctgagttcc gagccgcccc attgcaaggc
2100

55 atgctgcctg gcttgctggc acctctcagg accctctctg gaacccctga agttcactca
2160

aacaaaagag atatcatctt tcttttggat ggatcagcca acgttggaaa aaccaatttc
 2220

5 ccttatgtgc gcgactttgt aatgaaccta gttaacagcc ttgatattgg aaatgacaat
 2280

attcgtgttg gtttagtgca atttagtgac actcctgtaa cggagttctc tttaaacaca
 2340

10 taccagacca agtcagatat ccttggtcat ctgaggcagc tgcagctcca gggagggttcg
 2400

ggctgaaca caggctcagc cctaagctat gtctatgcc accacttcac ggaagctggc
 15 2460

ggacgagga tccgtgaaca cgtgccgcag ctctgtcttc tgctcacagc tgggcagtct
 2520

20 gaggactcct atttgcaagc tgccaacgcc ttgacacgcg cgggcacccct gactttttgt
 2580

gtgggagcta gccaggcgaa taaggcagag cttgagcaga ttgcttttaa cccaagcctg
 2640

25 gtgtatctca tggatgattt cagctccctg ccagctttgc ctcagcagct gattcagccc
 2700

ctaaccacat atgttagtgg aggtgtggag gaagtaccac tcgctcagcc agagagcaag
 2760

30 cgagacattc tgttcctctt tgacggctca gccaatcttg tgggccagtt ccctgttgtc
 2820

cgtgactttc tctacaagat tatcgatgag ctcaatgtga agccagaggg gacccgaatt
 35 2880

gcggtggctc agtacagcga tgatgtcaag gtggagtccc gttttgatga gcaccagagt
 2940

40 aagcctgaga tcttgaatct tgtgaagaga atgaagatca agacgggcaa agccctcaac
 3000

ctgggctacg cgctggacta tgcacagagg tacatttttg tgaagtctgc tggcagccgg
 3060

45 atcgaggatg gagtgttca gttcctggtg ctgctggtcg caggaaggtc atctgaccgt
 3120

gtggatgggc cagcaagtaa cctgaagcag agtgggggtt tgcctttcat cttccaagcc
 50 3180

aagaacgcag accctgctga gttagagcag atcgtgctgt ctccagcgtt tatcctggct
 3240

55 gcagagtcgc ttcccaagat tggagatctt catccacaga tagtgaatct cttaaaatca
 3300

gtgcacaacg gagcaccagc accagtttca ggtgaaaagg acgtggtggt tctgcttgat
3360

5 ggctctgagg gcgtcaggag cggcttccct ctgttgaaag agtttgtcca gagagtgggtg
3420

gaaagcctgg atgtgggcca ggaccgggtc cgcggtggccg tgggtgcagta cagcgaccgg
3480

10 accaggcccg agttctacct gaattcatac atgaacaagc aggacgtcgt caacgctgtc
3540

cgccagctga ccctgctggg agggccgacc cccaacaccg gggccgccct ggagtttgtc
3600

15 ctgaggaaca tcctgggtcag ctctgcggga agcaggataa cagaagggtg gccccagctg
3660

ctgatcgtcc tcacggccga caggctctggg gatgatgtgc ggaaccctc cgtgggtcgtg
3720

aagaggggtg gggctgtgcc cattggcatt ggcacgga acgctgacat cacagagatg
3780

25 cagaccatct ccttcatccc ggactttgcc gtggccattc ccaccttctg ccagctgggg
3840

accgtccaac aggtcatctc tgagaggggtg acccagctca cccgcgagga gctgagcagg
3900

30 ctgcagccgg tgttgagcc tctaccgagc ccagggtgtg gtggcaagag ggacgtggtc
3960

tttctcatcg atgggtccca aagtgcggg cctgagttcc agtacgttcg caccctcata
4020

gagaggtggtg ttgactacct ggacgtgggc tttgacacca cccgggtggc tgtcatccag
4080

40 ttcagcgatg accccaaggc ggagttcctg ctgaacgcc attccagcaa ggatgaagtg
4140

cagaacgcgg tgcagcggct gaggcccaag ggagggcggc agatcaacgt gggcaatgcc
4200

45 ctggagtagc tgtccaggaa catcttcaag agggccctgg ggagccgcat tgaagagggc
4260

gtcccacagt tcctggctct catctcgtct ggaaagtctg acgatgaggt ggtcgtcccg
4320

50 gcggtggagc tcaagcagtt tggcgtggcc cctttcacga tcgccaggaa cgcagaccag
4380

gaggagctgg tgaagatctc gctgagcccc gaatatgtgt tctcggtgag caccttccgg
4440

gagctgcccc gcctggagca gaaactgctg acgcccata cgaccctgac ctcagagcag
4500

5 atccagaagc tcttagccag cactcgctat ccacctccag cagttgagag tgatgctgca
4560

gacattgtct ttctgatcga cagctctgag ggagttaggc cagatggctt tgcacatatt
4620

10 cgagattttg ttagcaggat tgttcgaaga ctcaacatcg gccccagtaa agtgagagtt
4680

ggggtcgtgc agttcagcaa tgatgtcttc ccagaattct atctgaaaac ctacagatcc
15 4740

caggccccgg tgctggacgc catacggcgc ctgaggctca gaggggggtc cccactgaac
4800

20 actggcaagg ctctcgaatt tgtggcaaga aacctctttg ttaagtctgc ggggagtcgc
4860

atagaagacg gggtgcccca acacctggtc ctggctcctgg gtggaaaatc ccaggacgat
4920

25 gtgtccaggt tcgccaggt gatccgttcc tcgggcattg tgagtttagg ggtaggagac
4980

cggaacatcg acagaacaga gctgcagacc atcaccaatg accccagact ggtcttcaca
30 5040

gtgcgagagt tcagagagct tcccaacata gaagaaagaa tcatgaactc gtttggaacc
5100

35 tccgcagcca ctctgcacc tccaggggtg gacaccctc ctcttcacg gccagagaag
5160

aagaaagcag acattgtgtt cctgttgat ggttccatca acttcaggag ggacagtttc
5220

40 caggaagtgc ttcgttttgt gtctgaaata gtggacacag tttatgaaga tggcgactcc
5280

atccaagtgg ggcttgtcca gtacaactct gacccactg acgaattctt cctgaaggac
5340

45 ttctctacca agaggcagat tattgacgcc atcaacaaag tggctacaa agggggaaga
5400

cacgccaaca ctaagggtgg ccttgagcac ctgcgggtaa accactttgt gcctgaggca
50 5460

ggcagccgcc tggaccagcg ggtccctcag attgcctttg tgatcacggg aggaaagtcg
5520

55 gtggaagatg cacaggatgt gagcctggcc ctcaccaga ggggggtcaa agtgtttgct
5580

gttggagtga ggaatatcga ctcgaggag gttggaaaga tagcgtccaa cagcgccaca
5640

5 gcgttccgcg tgggcaacgt ccaggagctg tccgaactga gcgagcaagt tttggaaact
5700

ttgcatgatg cgatgcatga aaccctttgc cctggtgtaa ctgatgctgc caaagcttgt
5760

10 aatctggatg tgattctggg gtttgatggt tctagagacc agaattgttt tgtggcccag
5820

aagggttcg agtccaaggt ggacgccatc ttgaacagaa tcagccagat gcacagggtc
15 5880

agctgcagcg gtggccgctc gccaccctg cgtgtgtcag tggtgccaa cacgccctcg
5940

20 ggcccgttg aggcctttga ctttgacgag taccagccag agatgctcga gaagtccgg
6000

aacatgcgca gccagcacc ctacgtcctc acggaggaca ccctgaaggt ctacctgaac
6060

25 aagttcagac agtcctcgcc ggacagcgtg aagggtgtca ttcattttac tgatggagca
6120

gacggagatc tggctgattt acacagagca tctgagaacc tccgccaaga aggagtccgt
30 6180

gccttgatcc tggtgggcct tgaacgagtg gtcaacttgg agcggctaata gcattctggag
6240

35 tttgggagc ggtttatgta tgacaggccc ctgaggctta acttgctgga cttggattat
6300

gaactagcgg agcagcttga caacattgcc gagaaagctt gctgtggggg tccctgcaag
6360

40 tgctctgggc agaggggaga ccgcggggcc atcggcagca tcggggccaaa gggatttccct
6420

ggagaagacg gctaccgagg ctatcctggt gatgaggggt gacccggtga gcgtggtccg
45 6480

cctggtgtga acggcactca aggtttccag ggctgcccgg gccagagagg agtaaaaggc
6540

50 tctcggggat tcccaggaga gaaggcgaa gtaggagaaa ttggactgga tggctctggat
6600

ggtgaagatg gagacaaagg attgcctggt tcttctggag agaaaggga tcctggaaga
6660

55 aggggtgata aaggacctcg aggagagaaa ggagaaagag gagatgttgg gattcgaggg
6720

gacccgggta acccaggaca agacagccag gagagaggac ccaaaggaga aaccgggtgac
 6780

5 ctcggcccca tgggtgtccc agggagagat ggagtacctg gaggacctgg agaaactggg
 6840

aagaatgggtg gctttggccg aaggggaccc cccggagcta agggcaacaa gggcggctct
 6900

10 ggccagccgg gctttgaggg agagcagggg accagagggtg cacagggccc agctggctct
 6960

gctggtcctc cagggctgat aggagaacaa ggcatttctg gacctagggg aagcggaggt
 7020

15 gccctggcg ctcttgaga acgaggcaga accggtccac tgggaagaaa ggtgagccc
 7080

20 ggagagccag gaccaaagg aggaatcggg aaccggggcc ctctgggga gacgggagat
 7140

gacgggagag acggagtgg cagtgaagga cgcagaggca aaaaaggaga aagaggattt
 7200

25 cctggatacc caggaccaa gggtaaccca ggtgaacctg ggctaatgg aacaacagga
 7260

cccaaaggca tcagaggccg aaggggaaat tcgggacctc cagggatagt tggacagaag
 7320

30 gggagacctg gctaccagg accagctggt ccaaggggca acaggggca ctccatcgat
 7380

caatgtgcc tcattcaaag catcaaagat aaatgccctt gctgttacgg gccctggag
 7440

tgccccgtct tccaacaga actagccttt gctttagaca cctctgaggg agtcaacaa
 7500

40 gacactttcg gccggatgcg agatgtggtc ttgagtattg tgaatgtcct gaccattgct
 7560

gagagcaact gcccgacggg ggcccgggtg gctgtggtca cctacaacaa cgaggtgacc
 7620

45 acggagatcc ggtttgctga ctccaagagg aagtcggtcc tcctggacaa gattaagaac
 7680

cttcaggtgg ctctgacatc caaacagcag agtctggaga ctgccatgtc gtttgtggcc
 7740

50 aggaacacat ttaagcgtgt gaggaacgga ttcctaata ggaagtggc tgttttcttc
 7800

agcaacacac ccacaagagc atccccacag ctgagagagg ctgtgctcaa actctcagat
 7860

gcggggatca ccccttgtt ccttacaagg caggaagacc ggcagctcat caacgctttg
7920

5 cagatcaata acacagcagt ggggcatgcg cttgtcctgc ctgcaggag agacctcaca
7980

gacttcctgg agaatgtcct cacgtgtcat gtttgcttgg acatctgcaa catcgaccca
8040

10 tcctgtggat ttggcagttg gaggccttcc ttcagggaca ggagagcggc agggagtgtat
8100

gtggacatcg acatggcttt catcttagac agcgctgaga ccaccaccct gttccagttc
8160

15 aatgagatga agaagtacat agcgctacctg gtcagacaac tggacatgag cccagatccc
8220

aaggcctccc agcacttcgc cagagtggca gttgtgcagc acgcgccctc tgagtccgtg
8280

gacaatgcca gcatgccacc tgtgaaggty gaattctccc tgactgacta tggctccaag
8340

25 gagaagctgg tggacttcct cagcagggga atgacacagt tgcagggaac cagggcctta
8400

ggcagtgccca ttgaatacac catagagaat gtctttgaaa gtgccccaaa cccacgggac
8460

30 ctgaaaattg tggtcctgat gctgacgggc gaggtgccgg agcagcagct ggaggaggcc
8520

cagagagtca tcctgcaggc caaatgcaag ggctacttct tcgtggctcct gggcattggc
8580

35 aggaaggatga acatcaagga ggtatacacc ttgccagtg agccaaacga cgtcttcttc
8640

aaattagtgg acaagtccac cgagctcaac gaggagcctt tgatgcgctt cgggaggctg
8700

ttgccgtcct tcgtcagcag tgaaaatgct ttttacttgt cccagatat caggaaacag
8760

45 tgtgattggt tccaagggga ccaaccaca aagaaccttg tgaagtttgg tcacaaaca
8820

gtaaatgttc cgaataacgt tacttcaagt cctacatcca acccagtgac gacaacgaag
8880

50 ccggtgacta cgacgaagcc ggtgaccacc acaacaaagc ctgtaaccac cacaacaaag
8940

cctgtgacta ttataaatca gccatctgtg aagccagccg ctgcaaagcc ggcccctgcg
9000

aaacctgtgg ctgccaagcc tgtggccaca aagacggcca ctgttagacc cccagtggcg
 9060
 5 gtgaagccag caacagcagc gaagcctgta gcagcaaagc cagcagctgt aagaccccc
 9120
 gctgtgtctg caaaaccagt ggcgaccaag cctgaggctc ctaggccaca ggcagccaaa
 9180
 10 ccagctgcca ccaagccagc caccactaag cccgtgggta agatgctccg tgaagtccag
 9240
 gtgtttgaga taacagagaa cagcgccaaa ctccactggg agaggcctga gcccccggt
 15 9300
 ccttattttt atgacctcac cgtcacctca gcccatgac agtccctggg tctgaagcag
 9360
 20 aacctcacgg tcacggaccg cgtcattgga ggcctgctcg ctgggcagac ataccatgtg
 9420
 gctgtggtct gctacctgag gtctcaggtc agagccacct accacggaag tttcagtaca
 9480
 25 aagaaatctc agccccacc tccacagcca gcaaggctcag cttctagttc aaccatcaat
 9540
 ctaatggtga gcacagaacc attggctctc actgaaacag atatatgcaa gttgccgaaa
 30 9600
 gacgaaggaa cttgcaggga tttcatatta aaatgggtact atgatccaaa caccaaaagc
 9660
 35 tgtgcaagat tctggtatgg aggttgtggt ggaaacgaaa acaaatttgg atcacagaaa
 9720
 gaatgtgaaa aggtttgcgc tcctgtgctc gccaaacccg gagtcacag tgtgatggga
 9780
 40 acctaagcgt ggtgggcca catcatatac ctcttgaaga agaaggagtc agccatcgcc
 9840
 aacttgtctc tgtagaagct ccgggtgtag attcccttgc actgtatcat ttcattgcttt
 45 9900
 gatttacact cgaactcggg agggaacatc ctgctgcatg acctatcagt atggtgctaa
 9960
 50 tgtgtctgtg gaccctcgct ctctgtctcc agcagttctc tcgaatactt tgaatgttgt
 10020
 gtaacagtta gccactgctg gtgtttatgt gaacattcct atcaatccaa attccctctg
 10080
 55 gagtttcatg ttatgcctgt tgcaaggcaa tgtaaagtct agaaaataat gcaaatgtca
 10140

cggctactct atatactttt gcttggttca tttttttcc cttttagtta agcatgactt
10200

5 tagatgggaa gcctgtgtat cgtggagaaa caagagacca actttttcat tccctgcccc
10260

caatttccca gactagattt caagctaatt ttctttttct gaagcctcta acaaatgac
10320

10 tagttcagaa ggaagcaaaa tcccttaatc tatgtgcacc gttgggacca atgccttaat
10380

taaagaattt aaaaaagttg taatagagaa tatttttggc attcctctca atgttgtgtg
10440

15 tttttttttt ttgtgtgctg gagggagggg atttaatttt aatttttaaaa tgtttaggaa
10500

atttatacaa agaaactttt taataaagta tattgaaagt ttataaaaaa aaaaaaaa
10558

20

25

<210> 25

30 <211> 2133

<212> DNA

<213> Homo sapiens

35

<400> 25

40 cgggagagcg cgctctgcct gccgcctgcc tgcttgcac tgagggttcc cagcaccatg 60
agggcctgga tcttctttct cctttgcctg gccgggaggg ccttggcagc ccctcagcaa
120

45 gaagccctgc ctgatgagac agaggtggtg gaagaaactg tggcagaggt gactgaggta
180

tctgtgggag ctaatcctgt ccaggtggaa gtaggagaat ttgatgatgg tgcagaggaa
240

50 accgaagagg aggtggtggc ggaaaatccc tgccagaacc accactgcaa acacggcaag
300

gtgtgcgagc tggatgagaa caacaccccc atgtgcgtgt gccaggaccc caccagctgc
360

55

ccagccccc ttggcgagtt tgagaaggtg tgcagcaatg acaacaagac cttcgactct
420

5 tcctgccact tctttgccac aaagtgcacc ctggagggca ccaagaaggg ccacaagctc
480

cacctggact acatcgggcc ttgcaaatac atccccctt gcctggactc tgagctgacc
540

10 gaattcccc tgcgcatgcg ggactggctc aagaacgtcc tggtcaccct gtatgagagg
600

gatgaggaca acaaccttct gactgagaag cagaagctgc gggatgaaga gatccatgag
660

15 aatgagaagc gcctggaggc aggagaccac cccgtggagc tgctggcccg ggacttcgag
720

aagaactata acatgtacat cttccctgta cactggcagt tcggccagct ggaccagcac
780

ccattgacg ggtacctctc ccacaccgag ctggctccac tgcgtgctcc cctcatcccc
840

25 atggagcatt gcaccaccgc ctttttcgag acctgtgacc tggacaatga caagtacatc
900

gccctggatg agtgggcccg ctgcttcggc atcaagcaga aggatatcga caaggatctt
960

30 gtgatctaaa tccactcctt ccacagtacc ggattctctc tttaacctc ccttcgtgt
1020

ttcccccaat gtttaaaatg tttggatggt ttgttgttct gcctggagac aaggtgctaa
1080

catagattta agtgaatata ttaacggtgc taaaaatgaa aattctaacc caagacatga
1140

40 cattcttagc tgtaacttaa ctattaaggc cttttccaca cgcattaata gtcccatttt
1200

tctcttgcca tttgtagctt tgcccattgt cttattggca catgggtgga cacggatctg
1260

45 ctgggctctg ccttaaacac acattgcagc ttcaactttt ctcttttagt ttctgtttga
1320

aactaatact taccgagtca gactttgtgt tcatttcatt tcagggtctt ggctgcctgt
1380

50 gggcttcccc aggtggcctg gaggtgggca aagggaagta acagacacac gatgttgtca
1440

aggatggttt tgggactaga ggctcagtg tgggagagat ccctgcagaa tccaccaacc
1500

agaacgtggt ttgcctgagg ctgtaactga gagaaagatt ctggggctgt cttatgaaaa
1560

5 tatagacatt ctcacataag cccagttcat caccatttcc tcctttacct ttcagtgcag
1620

tttcttttca cattaggctg ttggttcaaa cttttgggag cacggactgt cagttctctg
1680

10 ggaagtgggc agcgcatcct gcagggttc tcctcctctg tcttttgag aaccagggct
1740

cttctcaggg gctctagga ctgccaggct gtttcagcca ggaaggcca aatcaagagt
1800

15 gagatgtaga aagttgtaaa atagaaaaag tggagttggt gaatcggtt ttctttcctc
1860

acatttgat gattgtcata aggttttttag catgttctc cttttcttca ccctccctt
1920

tgttcttcta ttaatcaaga gaaacttcaa agttaatggg atggtcggat ctcacaggct
1980

25 gagaactcgt tcacctcaa gcatttcatg aaaaagctgc ttcttattaa tcatacaaac
2040

tctcaccatg atgtgaagag tttcacaaat ctttcaaaat aaaaagtaat gacttagaaa
2100

30 ctgaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa
2133

35 <210> 26

<211> 2691

40 <212> DNA

<213> Homo sapiens

45 <400> 26

gcttgcccggt cggtcgctag ctgcgtcggt gcgcgtcgtc ccgctccatg gcgctcttcg 60

50 tgcggctgct ggctctcgcc ctggctctgg ccctgggccc cgccgcgacc ctggcgggtc
120

ccgccaaagtc gccctaccag ctgggtgctgc agcacagcag gctccggggc cgccagcacg
180

55

EP 1 439 393 A2

gccccaacgt gtgtgctgtg cagaaggtta ttggcactaa taggaagtac ttcaccaact
240

5 gcaagcagt gtaacaaagg aaaatctgtg gcaaatcaac agtcatcagc tacgagtgtc
300

gtcctggata tgaaaaggtc cctggggaga agggctgtcc agcagcccta ccactctcaa
360

10 acctttacga gaccctggga gtcgttggat ccaccaccac tcagctgtac acggaccgca
420

cggagaagct gaggcctgag atggaggggc ccggcagctt caccatcttc gcccttagca
480

15 acgaggcctg ggctccttg ccagctgaag tgctggactc cctggtcagc aatgtcaaca
540

20 ttgagctgct caatgccctc cgctaccata tgggtgggcag gcgagtcctg actgatgagc
600

tgaaacacgg catgaccctc acctctatgt accagaattc caacatccag atccaccact
660

25 atcctaattg gattgtaact gtgaactgtg cccggctcct gaaagccgac caccatgcaa
720

ccaacggggg ggtgcacctc atcgataagg tcatctccac catcaccaac aacatccagc
780

30 agatcattga gatcgaggac acctttgaga cccttcgggc tgctgtggct gcatcagggc
840

tcaacacgat gcttgaaggt aacggccagt acacgctttt ggccccgacc aatgaggcct
900

35 tcgagaagat ccctagttag actttgaacc gtatcctggg cgaccagaa gccctgagag
960

40 acctgctgaa caaccacatc ttgaagtcag ctatgtgtgc tgaagccatc gttgcggggc
1020

tgtctgtaga gaccctggag ggcacgacac tggaggtggg ctgcagcggg gacatgctca
1080

45 ctatcaacgg gaaggcgatc atctccaata aagacatcct agccaccaac ggggtgatcc
1140

actacattga tgagctactc atcccagact cagccaagac actatittgaa ttggctgcag
1200

50 agtctgatgt gtccacagcc attgacctt tcagacaagc cggcctcggc aatcatctct
1260

55 ctggaagtga gcggttgacc ctctggctc ccctgaattc tgtattcaaa gatggaacct
1320

ctccaattga tgcccataca aggaatttgc ttcggaacca cataattaaa gaccagctgg
1380

5 cctctaagta tctgtaccat ggacagaccc tggaaactct gggcggcaaa aaactgagag
1440

tttttgttta tcgtaatagc ctctgcattg agaacagctg catcgcggcc cacgacaaga
1500

10 gggggaggta cgggaccctg ttcacgatgg accgggtgct gacccccca atggggactg
1560

tcattgatgt cctgaaggga gacaatcgct ttagcatgct ggtagctgcc atccagtctg
1620

15 caggactgac ggagaccctc aaccgggaag gagtctacac agtccttctg cccacaaatg
1680

20 aagccttccg agccctgcc ccaagagaac ggagcagact cttgggagat gccaaggaac
1740

ttgccaacat cctgaaatac cacattggtg atgaaatcct ggtagcgga ggcacgggg
1800

25 ccctgggtgcg gctaaagtct ctccaagggtg acaagctgga agtcagcttg aaaaacaatg
1860

tggtgagtgt caacaaggag cctgttgccg agcctgacat catggccaca aatggcgtgg
1920

30 tccatgtcat caccaatggt ctgcagcctc cagccaacag acctcaggaa agaggggatg
1980

aacttgacga ctctgcgctt gagatcttca aacaagcatc agcgttttcc agggcttccc
2040

35 agaggtctgt gcgactagcc cctgtctatc aaaagttatt agagaggatg aagcattagc
2100

40 ttgaagcact acaggaggaa tgcaccacgg cagctctccg ccaatttctc tcagatttcc
2160

acagagactg tttgaatggt ttcaaaacca agtatcacac tttaatgtac atgggcccga
2220

45 ccataatgag atgtgagcct tgtgcatgtg ggggaggagg gagagagatg tactttttta
2280

atcatgttcc ccctaaacat ggctgttaac cactgcatg cagaaacttg gatgtcactg
2340

50 cctgacattc acttccagag aggacctatc ccaaatgtgg aattgactgc ctatgccaa
2400

55 tccctggaaa aggagcttca gtattgtggg gtcataaaa catgaatcaa gcaatccagc
2460

ctcatgggaa gtcctggcac agtttttgta aagcccttgc acagctggag aaatggcatc
2520

5 attataagct atgagttgaa atgttctgtc aaatgtgtct cacatctaca cgtggcttgg
2580

aggcttttat ggggccctgt ccaggtagaa aagaaatggg atgtagagct tagatttccc
2640

10 tattgtgaca gagccatggg gtgtttgtaa taataaaacc aaagaaacat a
2691

15 <210> 27

<211> 8027

20 <212> DNA

<213> Homo sapiens

25 <400> 27

acgcccgcgc cggctgtgct gcacaggggg aggagaggga accccaggcg cgagcgggaa 60

30 gaggggacct gcagccacaa cttctctggg cctctgcac cttctgtcc ctccaccctg
120

ccccttcccc accctctggc cccaccttc ttggaggcga caacccccgg gaggcattag
180

35 aagggatttt tcccgcagtt gcgaagggaa gcaaacttgg tggcaacttg cctcccgggt
240

cgggcgtctc tccccaccg tctcaacatg cttaggggtc cggggcccg gctgctgctg
300

40 ctggccgtcc agtgccctggg gacagcgggt cctccacgg gagcctcgaa gagcaagagg
360

caggctcagc aaatggttca gcccagtc cgggtggctg tcagtcaaag caagcccggg
420

tgttatgaca atggaaaaca ctatcagata aatcaacagt gggagcggac ctacctaggc
480

50 aatgcgttgg tttgtacttg ttatggagga agccgaggtt ttaactgcga gagtaaacct
540

gaagctgaag agacttgctt tgacaagtac actgggaaca cttaccgagt ggggtgacact
600

55

tatgagcgtc ctaaagactc catgatctgg gactgtacct gcatcggggc tgggcgaggg
 660
 5 agaataagct gtaccatcgc aaaccgctgc catgaagggg gtcagtccta caagattggt
 720
 10 gacacctgga ggagaccaca tgagactggt ggttacatgt tagagtgtgt gtgtcttggt
 780
 aatggaaaag gagaatggac ctgcaagccc atagctgaga agtggtttga tcatgctgct
 840
 15 gggacttcct atgtggtcgg agaaacgtgg gagaagccct accaaggctg gatgatggta
 900
 gattgtactt gcctgggaga aggcagcgga cgcatactt gcacttctag aaatagatgc
 960
 20 aacgatcagg acacaaggac atcctataga attggagaca cctggagcaa gaaggataat
 1020
 cgaggaaaacc tgctccagtg catctgcaca ggcaacggcc gaggagagtg gaagtgtgag
 1080
 25 aggcacacct ctgtgcagac cacatcgagc ggatctggcc ccttcaccga tgttcgtgca
 1140
 gctgtttacc aaccgcagcc tcacccccag cctcctccct atggccactg tgtcacagac
 1200
 30 agtgggtgtg tctactctgt ggggatgcag tggctgaaga cacaaggaaa taagcaaag
 1260
 35 ctttgacagt gcctgggcaa cggagtcagc tgccaagaga cagctgtaac ccagacttac
 1320
 ggtggcaact caaatggaga gccatgtgtc ttaccattca cctacaatgg caggacgttc
 1380
 40 tactcctgca ccacggaagg gcgacaggac ggacatcttt ggtgcagcac aacttcgaat
 1440
 tatgagcagg accagaaata ctctttctgc acagaccaca ctgttttggt tcagactcga
 1500
 45 ggaggaaatt ccaatggtgc cttgtgccac ttccccttcc tatacaacaa ccacaattac
 1560
 actgattgca cttctgaggg cagaagagac aacatgaagt ggtgtgggac cacacagaac
 1620
 50 tatgatgccg accagaagtt tgggttctgc cccatggctg cccacgagga aatctgcaca
 1680
 55 accaatgaag gggtcatgta ccgcattgga gatcagtggg ataagcagca tgacatgggt
 1740

cacatgatga ggtgcacgtg tgttggaat ggtcgtggg aatggacatg cattgcctac
 1800
 5 tgcgagcttc gagatcagtg cattgttgat gacatcactt acaatgtgaa cgacacattc
 1860
 cacaagcgtc atgaagaggg gcacatgctg aactgtacat gcttcggta gggtcggggc
 1920
 10 aggtggaagt gtgatccgt cgaccaatgc caggattcag agactgggac gttttatcaa
 1980
 attggagatt catgggagaa gtatgtgcat ggtgtcagat accagtgcta ctgctatggc
 2040
 15 cgtggcattg gggagtggca ttgccaacct ttacagacct atccaagctc aagtggctct
 2100
 20 gtcgaagtat ttatcactga gactccgagt cagcccaact cccaccccat ccagtggaa
 2160
 gcaccacagc catctcacat ttccaagtac attctcaggt ggagacctaa aaattctgta
 2220
 25 ggccgttga aggaagctac cataccaggc cacttaaact cctacacat caaaggcctg
 2280
 aagcctggtg tggatatacga gggccagctc atcagcatcc agcagtacgg ccaccaagaa
 2340
 30 gtgactcgtt ttgacttcac caccaccagc accagcacac ctgtgaccag caacaccgtg
 2400
 acaggagaga cgactccctt ttctcctctt gtggccactt ctgaatctgt gaccgaaatc
 2460
 acagccagta gctttgtggt ctctgggtc tcagcttccg acaccgtgct gggattccgg
 2520
 40 gtggaatatg agctgagtga ggaggagat gagccacagt acctggtct tccaagcaca
 2580
 gccattctg tgaacatccc tgacctgctt cctggccgaa aatacattgt aaatgtctat
 2640
 45 cagatatctg aggatgggga gcagagtttg atcctgtcta cttcaciaac aacagcgct
 2700
 gatgccctc ctgaccgac tgtggacaa gttgatgaca cctcaattgt tgttcgctgg
 2760
 50 agcagacccc aggtcccat cacagggtac agaatagtct attcgccatc agtagaaggt
 2820
 55 agcagcacag aactcaacct tcctgaaact gcaaactccg tcacctcag tgacttgcaa
 2880

cctggtgttc agtataacat cactatctat gctgtggaag aaaatcaaga aagtacacct
 2940

5 gttgtcattc aacaagaaac cactggcacc ccacgctcag atacagtgcc ctctcccagg
 3000

gacctgcagt ttgtggaagt gacagacgtg aaggtcacca tcatgtggac accgcctgag
 3060

10 agtgcagtga ccggtaccg tgtggatgtg atccccgtca acctgcctgg cgagcacggg
 3120

cagaggctgc ccatcagcag gaacaccttt gcagaagtca ccgggctgtc ccctggggtc
 15 3180

acctattact tcaaagtctt tgcagtgagc catggggagg agagcaagcc tctgactgct
 3240

20 caacagacaa ccaaactgga tgctcccact aacctccagt ttgtcaatga aactgattct
 3300

actgtcctgg tgagatggac tccacctcgg gccagataa caggataccg actgaccgtg
 3360

25 ggccttaccg gaagaggcca gcccaggcag tacaatgtgg gtccctctgt ctccaagtac
 3420

cccctgagga atctgcagcc tgcactctgag tacaccgtat ccctcgtggc cataaagggc
 3480

30 aaccaagaga gcccacaaagc cactggagtc ttaccacac tgcagcctgg gagctctatt
 3540

ccaccttaca acaccgaggt gactgagacc accatcgtga tcacatggac gcctgctcca
 35 3600

agaattggtt ttaagctggg tgtacgacca agccaggag gagaggcacc acgagaagtg
 3660

40 acttcagact caggaagcat cgttgtgtcc ggcttgactc caggagtaga atacgtctac
 3720

accatccaag tcctgagaga tggacaggaa agagatgcgc caattgtaaa caaagtgggtg
 3780

45 acaccattgt ctccaccaac aaacttgcat ctggaggcaa accctgacac tggagtgtc
 3840

acagtctcct gggagaggag caccacccca gacattactg gttatagaat taccacaacc
 3900

50 cctacaaacg gccagcaggg aaattctttg gaagaagtgg tccatgtctga tcagagctcc
 3960

55 tgcacttttg ataacctgag tcccggcctg gagtacaatg tcagtgttta cactgtcaag
 4020

gatgacaagg aaagtgtccc tatctctgat accatcatcc cagctgttcc tcctcccact
 4080
 5 gacctgcat tcaccaacat tgggtccagac accatgcatg tcacctgggc tccaccccca
 4140
 tccattgatt taaccaactt cctggtgcat tactcacctg tgaaaaatga ggaagatgtt
 4200
 10 gcagagttgt caatttctcc ttcagacaat gcagtggctt taacaaatct cctgcctggt
 4260
 acagaatatg tagtgagtgt ctccagtgtc tacgaacaac atgagagcac acctcttaga
 4320
 15 ggaagacaga aaacaggtct tgattcccca actggcattg acttttctga tattactgcc
 4380
 aactctttta ctgtgcactg gattgctcct cgagccacca tcaactggta caggatccgc
 4440
 catcatcccg agcacttcag tgggagacct cgagaagatc ggtgtcccca ctctcggaat
 4500
 25 tccatcacc tcaccaacct cactccaggc acagagtatg tggtcagcat cgttgctctt
 4560
 aatggcagag aggaaagtcc cttattgatt ggccaacaat caacagtttc tgatgttccg
 4620
 30 agggacctgg aagtgtgtgc tgcgaccccc accagcctac tgatcagctg ggtgtcctt
 4680
 gctgtcacag tgagatatta caggatcact tacggagaaa caggaggaaa tagccctgtc
 4740
 35 caggagtcca ctgtgcctgg gagcaagtct acagctacca tcagcggcct taaacctgga
 4800
 40 gttgattata ccatcactgt gtatgctgtc actggccgtg gagacagccc cgcaagcagc
 4860
 aagccaattt ccattaatta ccgaacagaa attgacaaac catcccagat gcaagtgacc
 4920
 45 gatgttcagg acaacagcat tagtgtcaag tggctgcctt caagttcccc tgttactggt
 4980
 tacagagtaa ccaccactcc caaaaatgga ccaggaccaa caaaaactaa aactgcaggt
 5040
 50 ccagatcaaa cagaaatgac tattgaaggc ttgcagccca cagtggagta tgtggtagt
 5100
 55 gtctatgctc agaatccaag cggagagagt cagcctctgg ttcagactgc agtaaccaac
 5160

attgatcgcc ctaaaggact ggcattcact gatgtggatg tcgattccat caaaattgct
5220

5 tgggaaagcc cacaggggca agtttccagg tacaggggta cctactcgag ccctgaggat
5280

ggaatccatg agctattccc tgcacctgat ggtgaagaag aactgcaga gctgcaaggc
5340

10 ctcagaccgg gttctgagta cacagtcagt gtggttgcc tgcacgatga tatggagagc
5400

cagcccccta ttggaaccca gtccacagct attcctgcac caactgacct gaagttcact
15 5460

caggtcacac ccacaagcct gagcgcccag tggacaccac ccaatgttca gctcactgga
5520

20 tatcgagtgc gggtgacccc caaggagaag accggaccaa tgaaagaaat caaccttgct
5580

cctgacagct catccgtggg tgtatcagga cttatggtgg ccaccaaata tgaagtgagt
5640

25 gtctatgctc ttaaggacac ttgacaagc agaccagctc aggggtgtgt caccactctg
5700

gagaatgtca gcccaccaag aagggtcgt gtgacagatg ctactgagac caccatcacc
30 5760

attagctgga gaaccaagac tgagacgatc actggcttcc aagttgatgc cgttccagcc
5820

35 aatggccaga ctccaatcca gagaaccatc aagccagatg tcagaagcta caccatcaca
5880

ggtttacaac caggcactga ctacaagatc tacctgtaca ccttgaatga caatgctcgg
5940

40 agctcccctg tggtcacga cgccctccact gccattgatg caccatcaa cctgcgtttc
6000

ctggccacca cacccaattc cttgctggta tcatggcagc cgccacgtgc caggattacc
6060

45 ggctacatca tcaagtatga gaagcctggg tctcctccca gagaagtggc ccctcgcccc
6120

cgccctggtg tcacagaggc tactattact ggccctggaac cggaaccga atatacaatt
50 6180

tatgtcattg ccctgaagaa taatcagaag agcgagcccc tgattggaag gaaaaagaca
6240

55 gacgagcttc cccaactggg aacccttcca caccacaatc tcatgggacc agagatcttg
6300

gatgttcctt ccacagttca aaagaccctt ttcgtcacc accctgggta tgacactgga
 6360
 5 aatgggtattc agcttccttg cacttctggt cagcaaccca gtgttgggca acaaatgac
 6420
 tttgaggaac atggttttag gcggaccaca ccgcccacaa cggccacccc cataaggcat
 6480
 10 aggccaagac catacccgcc gaatgtagga caagaagctc tctctcagac aaccatctca
 6540
 tgggccccat tccaggacac ttctgagtac atcatttcat gtcacacctgt tggcactgat
 15 6600
 gaagaacctt tacagttcag ggttcctgga acttctacca gtgccactct gacaggcctc
 6660
 20 accagaggtg ccacctacaa catcatagtg gaggcactga aagaccagca gaggcataag
 6720
 gttcgggaag aggttggttac cgtgggcaac tctgtcaacg aaggcttgaa ccaacctacg
 6780
 25 gatgactcgt gctttgaccc ctacacagtt tcccattatg ccgttgagga tgagtgggaa
 6840
 cgaatgtctg aatcaggctt taaactgttg tgccagtgt taggcttttg aagtggctat
 30 6900
 ttcagatgtg attcatctag atggtgccat gacaatggtg tgaactacaa gattggagag
 6960
 35 aagtgggacc gtcagggaga aaatggccag atgatgagct gcacatgtct tgggaacgga
 7020
 aaaggagaat tcaagtgtga ccctcatgag gcaacgtgtt acgatgatgg gaagacatac
 7080
 40 cacgtaggag aacagtggca gaaggaatat ctcggtgcca tttgctcctg cacatgcttt
 7140
 ggaggccagc ggggctggcg ctgtgacaac tgccgcagac ctgggggtga acccagtccc
 45 7200
 gaaggcacta ctggccagtc ctacaaccag tattctcaga gataccatca gagaacaaac
 7260
 50 actaatgtta attgcccaat tgagtgttc atgcctttag atgtacaggc tgacagagaa
 7320
 gattcccgag agtaaatcat ctttccaatc cagaggaaca agcatgtctc tctgccaaga
 7380
 55 tccatctaaa ctggagtgat gttagcagac ccagcttaga gttcttcttt ctttcttaag
 7440

ccctttgctc tggaggaagt tctccagctt cagctcaact cacagcttct ccaagcatca
 7500
 5 ccctgggagt ttcctgaggg ttttctcata aatgagggct gcacattgcc tgttctgctt
 7560
 cgaagtattc aataccgctc agtatTTTaa atgaagtgat tctaagattt ggTTTgggat
 7620
 10 caataggaaa gcatatgcag ccaaccaaga tgcaaatggt ttgaaatgat atgacccaaa
 7680
 ttttaagtag gaaagtcacc caaacacttc tgctttcact taagtgtctg gcccgcaata
 15 7740
 ctgtaggaac aagcatgata ttgttactgt gatattTTTaa atatccacag tactcacttt
 7800
 20 ttccaaatga tcctagtaat tgcctagaaa tatctttctc ttacctgtta tttatcaatt
 7860
 tttccagta tttttatacg gaaaaaattg tattgaaaac acttagtatg cagttgataa
 7920
 25 gaggaatttg gtataattat ggtgggtgat tattttttat actgtatgtg ccaaagcttt
 7980
 actactgtgg aaagacaact gttttaataa aagatttaca ttccaca
 8027
 30
 35
 <210> 28
 <211> 5084
 40 <212> DNA
 <213> Homo sapiens
 45
 <400> 28
 agcaccacgg cagcaggagg tttcggctaa gttggaggta ctggccacga ctgcatgccc 60
 50 gcgcccgcga ggtgatacct ccgccggtga cccaggggct ctgcgacaca aggagtctgc
 120
 atgtctaagt gctagacatg ctcaagcttg tggatacgcg gactttgttg ctgcttgacg
 180
 55

taaccttatg cctagcaaca tgccaatctt tacaagagga aactgtaaga aagggccag
 240
 5 ccggagatag aggaccacgt ggagaaaggg gtccaccagg cccccaggc agagatggtg
 300
 aagatggtcc cacaggccct cctgggccac ctggctctcc tggccccct ggtctcggtg
 360
 10 ggaactttgc tgctcagtat gatggaaaag gagttggact tggccctgga ccaatgggct
 420
 taatgggacc tagaggccca cctgggtgcag ctggagcccc aggcctcaa ggtttccaag
 15 480
 gacctgctgg tgagcctggt gaacctggtc aaactgggcc tgcagggtgct cgtgggccag
 540
 20 ctggccctcc tggcaaggct ggtgaagatg gtcaccctgg aaaaccgga cgacctggtg
 600
 agagaggagt tggtggacca cagggtgctc gtggtttccc tggaaactct ggacttctg
 660
 25 gcttcaaagg cattagggga cacaatggtc tggatggatt gaagggacag cccggtgctc
 720
 ctggtgtgaa gggatgaacct ggtgcccctg gtgaaaatgg aactccaggt caaacaggag
 30 780
 cccgtgggct tcctgggtgag agaggacgtg ttgggtgccc tggcccagct ggtgcccgtg
 840
 35 gcagtgatgg aagtgtgggt cccgtgggtc ctgctgggcc cattgggtct gctggccctc
 900
 caggcttccc aggtgcccct ggccccaagg gtgaaattgg agctgttggt aacgctggtc
 960
 40 ctgctgggcc cgccgggtccc cgtgggtgaag tgggtcttcc aggcctctcc ggccccgttg
 1020
 gacctctgg taatcctgga gcaaacggcc ttactggtgc caagggtgct gctggccttc
 1080
 45 ccggcggtgc tggggctccc ggcctccctg gaccccgcg tattcctggc cctgttggtg
 1140
 ctgccggtgc tactggtgcc agaggacttg ttggtgagcc tgggccagct ggctccaaag
 50 1200
 gagagagcgg taacaagggt gagcccggct ctgctgggcc ccaaggctct cctgggtcca
 1260
 55 gtggtgaaga aggaagaga ggcctaata ggaagctgg atctgccggc cctccaggac
 1320

ctcctgggct gagaggtagt cctggttctc gtggtcttcc tggagctgat ggcagagctg
1380

5 gcgtcatggg ccctcctggt agtcgtggtg caagtggccc tgctggagtc cgaggaccta
1440

atggagatgc tggtcgccct ggggagcctg gtctcatggg acccagaggt cttcctggtt
1500

10 cccctggaaa tatcgccccc gctggaaaag aaggtcctgt cggcctccct ggcacgcacg
1560

gcaggcctgg cccaattggc ccagctggag caagaggaga gcctggcaac attggattcc
1620

15 ctggacccaa aggccccact ggtgatcctg gcaaaaacgg tgataaaggt catgctggtc
1680

20 ttgctggtgc tcggggtgct ccaggtcctg atggaaacaa tggtgctcag ggacctcctg
1740

gaccacaggg tgttcaaggt ggaaaagggtg aacagggtcc cgctggtcct ccaggcttcc
1800

25 agggctctgc tggtccctca ggtcccgtg gtgaagtgg caaacagga gaaaggggtc
1860

tccatggtga gtttggctc cctggctcctg ctggtccaag aggggaacgc ggtccccag
1920

30 gtgagagtgg tgctgccggt cctactggtc ctattggaag ccgaggtcct tctggacccc
1980

cagggcctga tggaaacaag ggtgaacctg gtgtggttgg tgctgtgggc actgctggtc
2040

35 catctggtcc tagtggactc ccaggagaga ggggtgctgc tggcatacct ggaggcaagg
2100

40 gagaaaagg tgaacctggt ctcagaggtg aaattggtaa ccctggcaga gatggtgctc
2160

gtggtgctca tgggtgctga ggtgcccctg gtctgctgg agccacaggt gaccggggcg
2220

45 aagctggggc tgctggtcct gctggtcctg ctggtcctcg gggaagccct ggtgaacgtg
2280

gagaggtcgg tctgctggc cccaacggat ttgctggtcc ggctggtgct gctggtcaac
2340

50 cgggtgctaa aggagaaaga ggagccaaag ggctaagggt tgaaaacggt gttgttggtc
2400

55 ccacaggccc cgttggagct gctggcccag ctggtccaaa tgggtccccc ggtcctgctg
2460

gaagtcgtgg tgatggaggc cccctggta tgactggttt cctggtgct gctggacgga
 2520

5 ctggtcccc aggacctct ggtatttctg gccctcctgg tccccctggt cctgctggga
 2580

aagaagggt tcgtggctct cgtggtgacc aagggtccagt tggccgaact ggagaagtag
 2640

10 gtgcagttgg tccccctggc ttcgctggtg agaagggtcc ctctggagag gctggtactg
 2700

ctggacctcc tggcaactcca ggtcctcagg gtcttcttgg tgctcctggt attctgggtc
 15 2760

tccctggctc gagagggtgaa cgtggtctac ctggtgttgc tggtgctgtg ggtgaacctg.
 2820

20 gtctcttgg cattgccggc cctcctgggg cccgtggtcc tcctggtgct gtgggtagtc
 2880

ctggagtcaa cggtgctcct ggtgaagctg gtctgtgatg caaccctggg aacgatggtc
 2940

25 ccccaggctc cgatgggtcaa cccggacaca agggagagcg cggttaacct ggcaatattg
 3000

gtcccgttgg tgctgcaggt gcacctggtc ctcatggccc cgtgggtcct gctggcaaac
 30 3060

atggaaaacc tggtgaaact ggtccttctg gtccctgttg tcctgctggt gctgttgccc
 3120

35 caagagggtc tagtggtcca caaggcatc gtggcgataa gggagagccc ggtgaaaagg
 3180

ggcccagagg tcttcctggc ttaaaggac acaatggatt gcaaggctct cctggtatcg
 3240

40 ctggtcacca tgggatcaa ggtgctcctg gctccgtggg tcctgctggt cctaggggcc
 3300

ctgctggtcc ttctggccct gctggaaaag atggtcgcac tggacatcct ggtacggttg
 3360

45 gacctgctgg cattcgaggc cctcagggtc accaaggccc tgctggcccc cctggtcccc
 3420

ctggccctcc tggacctcca ggtgtaagcg gtggtggtta tgactttggt tacgatggag
 50 3480

acttctacag ggctgaccag cctcgtcag caccttctct cagaccaag gactatgaag
 3540

55 ttgatgctac tctgaagtct ctcaacaacc agattgagac ccttcttact cctgaaggct
 3600

ctagaaagaa cccagctcgc acatgccgtg acttgagact cagccacca gagtggagca
 3660
 5 gtggttacta ctggattgac cctaaccaag gatgcactat ggatgctatc aaagtatact
 3720
 gtgatttctc tactggcgaa acctgtatcc gggcccaacc tgaaaacatc ccagccaaga
 3780
 10 actggtatag gagctccaag gacaagaaac acgtctggct aggagaaact atcaatgctg
 3840
 gcagccagtt tgaatataat gtagaaggag tgacttccaa ggaaatggct acccaacttg
 3900
 15 ccttcacgct cctgctggcc aactatgcct ctcagaacat cacctaccac tgcaagaaca
 3960
 20 gcattgcata catggatgag gagactggca acctgaaaaa ggctgtcatt ctacagggtc
 4020
 ctaatgatgt tgaacttggt gctgagggca acagcagggt cacttacact gttctttag
 4080
 25 atggctgctc taaaaagaca aatgaatggg gaaagacaat cattgaatac aaaacaaata
 4140
 agccatcacg cctgcccttc cttgatattg cacctttgga catcgggtgt gctgaccatg
 4200
 30 aattctttgt ggacattggc ccagtctgtt tcaaataaat gaactcaatc taaattaaaa
 4260
 aagaaagaaa ttgaaaaaa ctttctcttt gccatttctt cttcttcttt tttaactgaa
 4320
 35 agctgaatcc ttccatttct tctgcacatc tacttgctta aattgtgggc aaaagagaaa
 4380
 40 aagaaggatt gatcagagca ttgtgcaata cagtttcatt aactccttc cccgctcccc
 4440
 caaaaatttg aatttttttt tcaacactct tacacctgtt atggaaaatg tcaacctttg
 4500
 45 taagaaaacc aaaataaaaa ttgaaaaata aaaaccataa acatttgcac cacttggtggc
 4560
 ttttgaatat ctccacaga gggaggttta aaacccaaac ttccaaagggt ttaaactacc
 4620
 50 tcaaaacact ttccatgag tgtgatccac attgttaggt gctgacctag acagagatga
 4680
 55 actgaggtcc ttgttttgtt ttgttcataa tacaaagggt ctaattaata gtatttcaga
 4740

tacttgaaga atgttgatgg tgctagaaga atttgagaag aaatactcct gtattgagtt
4800

5 gtatcgtgtg gtgtatTTTT taaaaaattt gatttagcat tcatatTTTc catcttattc
4860

ccaattaaaa gtatgcagat tatttgccca aagttgtcct cttcttcaga ttcagcattt
4920

10 gttctttgcc agtctcattt tcatcttctt ccatggttcc acagaagctt tgtttcttgg
4980

gcaagcagaa aaattaaatt gtacctattt tgtatatgtg agatgtttaa ataaattgtg
5040

15 aaaaaaatga aataaagcat gtttggtttt caaaagaac atat
5084

20

25 <210> 29
<211> 595
<212> DNA

30 <213> Homo sapiens

35 <400> 29

gggcaaggct gggccgggaa gggcgtgggt tgaggagagg ctccagaccc gcacgccgcg 60

cgcacagagc tctcagcgcc gctcccagcc acagcctccc gcgcctcgct cagctccaac
40 120

atggcaaaaa tctccagccc tacagagact gagcgggtgca tcgagtcctt gattgctgtc
180

45 ttccagaagt atgctggaaa ggatggttat aactacactc tctccaagac agagttccta
240

agcttcatga atacagaact agctgccttc acaaagaacc agaaggaccc tgggtgcctt
300

50 gaccgcatga tgaagaaact ggacaccaac agtgatggtc agctagattt ctcaaatTT
360

cttaaatctga ttggtggcct agctatggct tgccatgact ccttcctcaa ggctgtccct
420

55

tcccagaagc ggacctgagg accccttggc cctggccttc aaaccaccc cctttccttc
480

5 cagcctttct gtcacatctt ccacagccca cccatcccct gagcacacta accacctcat
540

gcaggcccca cctgccaata gtaataaagc aatgtcactt ttttaaaaca tgaaa
595

10

<210> 30

15 <211> 2116

<212> DNA

<213> Homo sapiens

20

<400> 30

25 gtgaaggccg gcgcgctcgc cggccgaggt gggatcccga ggcctctcca gtccgccgag 60

ggcgcaccac cggcccgtct cggccgcccgc gccggggagg tggagcacga gcgcacgtgt
120

30 taggaccgga aagatggtga actatgcctg ggcagggcga agccagagga aactctggtg
180

gagggtccgta gcggctcctga cgtgcaaata ggtcgtccga cctgggtata ggggcgggct
240

35 ccaggcgagg cggctgacgc tctgaaaac ttgcgcgcgc gctcgcgcca ctgcgcccg
300

agcgatgaag atggtcgcgc cctggacgcg gttctactcc aacagctgct gcttggtgctg
360

40 ccatgtccgc accggcacca tctgctcgg cgtctggtat ctgatcatca atgctgtggt
420

actgttgatt ttattgagt ccctggctga tccgatcag tataactttt caagttctga
480

45 actgggaggt gactttgagt tcatggatga tgccaacatg tgcatcgcca ttgcgatttc
540

50 tcttctcatg atcctgatat gtgctatggc tacttacgga gcgtacaagc aacgcgcagc
600

ctggatcatc ccattcttct gttaccagat ctttgacttt gccctgaaca tgttggttgc
660

55

aatcactgtg cttatattatc caaactccat tcaggaatac atacggcaac tgcctcctaa
 720

5 ttttccctac agagatgatg tcatgtcagt gaatcctacc tgtttggtcc ttattattct
 780

tctgtttatt agcattatct tgacttttaa gggttacttg attagctgtg tttggaactg
 840

10 ctaccgatac atcaatggta ggaactcctc tgatgtcctg gtttatgtta ccagcaatga
 900

cactacggtg ctgctacccc cgtatgatga tgccactgtg aatggtgctg ccaaggagcc
 15 960

accgccacct tacgtgtctg cctaagcctt caagtgggag gagctgaggg cagcagcttg
 1020

20 actttgcaga catctgagca atagtctgtg tatttcactt ttgcatgag cctctctgag
 1080

cttgtttgtt gctgaaatgc tactttttaa aatttagatg ttagattgaa aactgtagtt
 1140

25 ttcaacatat gctttgctag aacactgtga tagattaact gtagaattct tcctgtacga
 1200

ttggggatat aatgggcttc actaaccttc cctaggcatt gaaacttccc ccaaactctga
 30 1260

tggacctaga agtctgcttt tgtacctgtg gggcccaaaa gttgggcatt tttctctctg
 1320

35 ttccctctct tttgaaaatg taaaataaaa ccaaaaatag acaacttttt cttcagccat
 1380

tccagcatag agaacaaaac cttatggaaa caggaatgtc aattgtgtaa tcattgttct
 1440

40 aattaggtaa atagaagtcc ttatgtatgt gttacaagaa tttccccac aacatccttt
 1500

atgactgaag ttcaatgaca gtttgtgttt gggtggtaaa ggattttctc catggcctga
 1560

45 attaagacca ttagaaagca ccaggccgtg ggagcagtga ccatctgctg actgttcttg
 1620

tggatcttgt gtccagggac atgggggtgac atgcctcgta tgtgttagag ggtggaatgg
 50 1680

atgtgtttgg cgctgcatgg gatctgggtc ccctcttctc ctggattcac atccccacc
 1740

55 agggcccgtt ttactaagt gttctgccct agattgggtc aaggaggtca tccaactgac
 1800

tttatcaagt ggaattggga tatatttgat atacttctgc ctaacaacat ggaaaaggg
 1860
 5 tttcttttcc ctgcaagcta catcctactg ctttgaactt ccaagtatgt ctagtcacct
 1920
 tttaaaatgt aaacattttc agaaaaatga ggattgcctt ccttgatgc gctttttacc
 1980
 10 ttgactacct gaattgcaag ggatttttat atattcatat gttacaaagt cagcaactct
 2040
 cctgttggtt cattattgaa tgtgctgtaa attaagttgt ttgcaattaa aacaaggttt
 15 2100
 gccacaaaa aaaaaa
 2116
 20
 <210> 31
 <211> 3583
 25 <212> DNA
 <213> Homo sapiens
 30
 <400> 31
 cgcgagcccg gccggcccag gcccgcgccc gcccgggccc tgagaggccc cggcaggtcc 60
 35 cggcccggcg gcggcagcca tggccggggg gccgggcccg ggggagcccg cagcccccg
 120
 cgcccagcac ttcttgtagc aggtgcccgc ctgggtcatg tgccgcttct acaaagtgat
 180
 40 ggacgccttg gagcccgccg actggtgcca gtgcgcccgc ctgatcgtgc gcgaccagac
 240
 cgagctgcgg ctgtgcgagc gctccgggca gcgcacggcc agcgtcctgt ggccctggat
 45 300
 caaccgaac gcccggtgtg ccgacctcgt gcacatcctc acgcacctgc agctgctccg
 360
 50 tgcgcgggac atcatcacag cctggcacc tcccgcccgc cttccgtccc caggcaccac
 420
 tgccccgagg cccagcagca tccctgcacc cgccgaggcc gaggcctgga gccccggaa
 480
 55

gttgccatcc tcagcctcca ccttcctctc ccagctttt ccaggctccc agaccatcc
540

5 agggcctgag ctggcctgg ttccaagccc tgcttccctg tggcctccac cgccatctcc
600

agcccttct tctaccaagc caggcccaga gagctcagtg tccctcctgc agggagcccg
660

10 cccctctccg ttttgctggc ccctctgtga gatttcccg ggcaccaca acttctcgga
720

ggagctcaag atcggggagg gtggctttgg gtgcgtgtac cgggcggtga tgaggaacac
15 780

ggtgtatgct gtgaagaggc tgaaggagaa cgctgacctg gagtggactg cagtgaagca
840

20 gagcttctg accgaggtgg agcagctgtc caggtttcgt caccacaaca ttgtggactt
900

tgctggctac tgtgctcaga acggcttcta ctgcctggtg tacggcttcc tgcccaacgg
960

25 ctccctggag gaccgtctcc actgccagac ccaggcctgc ccacctctc cctggcctca
1020

ggcactggac atccttctgg gtacagcccg ggcaattcag tttctacatc aggacagccc
1080

30 cagcctcatc catggagaca tcaagagttc caacgtcctt ctggatgaga ggctgacacc
1140

caagctggga gactttggcc tggcccgggt cagccgcttt gccgggtcca gccccagcca
35 1200

gagcagcatg gtggcccga cacagacagt gcggggcacc ctggcctacc tgcccagga
1260

40 gtacatcaag acgggaaggc tggctgtgga cacggacacc ttcagctttg ggggtgtagt
1320

gctagagacc ttggctggtc agagggctgt gaagacgcac ggtgccagga ccaagtatct
1380

45 gaaagacctg gtggaagagg aggctgagga ggctggagtg gctttgagaa gcaccagag
1440

cacactgcaa gcaggctctgg ctgcagatgc ctgggctgct cccatcgcca tgcagatcta
50 1500

caagaagcac ctggaccca ggcccgggcc ctgccacct gagctgggcc tgggcctggg
1560

55 ccagctggcc tgctgctgcc tgcaccgccg ggccaaaagg aggcctcta tgaccaggt
1620

gtacgagagg ctagagaagc tgcaggcagt ggtggcgggg gtgcccgggc atttgagggc
1680

5 cgccagctgc atccccctt cccgcagga gaactcctac gtgtccagca ctggcagagc
1740

ccacagtggg gctgctccat ggcagcccct ggcagcgcca tcaggagcca gtgccaggc
1800

10 agcagagcag ctgcagagag gcccacaacca gcccgaggag agtgacgaga gcctaggcgg
1860

cctctctgct gccctgcgct cctggcactt gactccaagc tgcctctgg acccagcacc
15 1920

cctcaggag gccggctgtc ctcaggggga cacggcagga gaatcgagct gggggagtgg
1980

20 cccaggatcc cggcccacag ccgtggaagg actggccctt ggcagctctg catcatcgtc
2040

gtcagagcca ccgcagatta tcatcaacct tgcccagacag aagatggtcc agaagctggc
2100

25 cctgtacgag gatggggccc tggacagcct gcagctgctg tcgtccagct ccctcccagg
2160

cttgggcctg gaacaggaca ggcagggggc cgaagaaagt gatgaatttc agagctgatg
2220

30 tgttcacctg ggcagatccc ccaaatacgg aagtcaaagt tctcatggtc agaagttctc
2280

atggtgcacg agtcctcagc actctgccgg cagtgggggt gggggcccat gccgcgggg
35 2340

gagagaagga ggtggccctg ctgttctagg ctctgtgggc ataggcaggc agagtggaac
2400

40 cctgcctcca tgccagcatc tgggggcaag gaaggctggc atcatccagt gaggaggctg
2460

gcgcatgttg ggaggctgct ggctgcacag acccgtagg ggaggagagg ggctgctgtg
2520

45 caggggtgtg gagtagggag ctggctcccc tgagagccat gcagggcgtc tgagcccag
2580

gcctctggca gcagctcttt gccatctct tggacagtg gccaccctgc acaatggggc
50 2640

cgacgaggcc tagggccctc ctacctgctt acaatttgga aaagtgtggc cgggtgcggt
2700

55 ggctcacgcc tgtaatccca gcactttggg aggccaaaggc aggaggatcg ctggagccca
2760

gtaggtcaag accagccagg gcaacatgat gagaccctgt ctctgccaaa aaatttttta
 2820

5 aactattagc ctggcgtggt agcgacgcc tgtggtccca gctgctgggg aggctgaagt
 2880

aggaggatca tttatgcttg ggaggtcgag gctgcagtga gtcattgattg tatgactgca
 2940

10 ctccagcctg ggtgacagag caagaccctg tttcaaaaag aaaaaccctg ggaaaagtga
 3000

agtatggctg taagtctcat ggttcagtcc tagcaagaag cgagaattct gagatcctcc
 15 3060

agaaagtoga gcagcaccca cctccaacct cgggccagtg tcttcaggct ttactgggga
 3120

20 cctgcgagct ggcctaattgt ggtggcctgc aagccaggcc atccctgggc gccacagacg
 3180

agctccgagc caggtcaggc ttcggaggcc acaagctcag cctcaggccc aggcactgat
 3240

25 tgtggcagag gggccactac ccaaggtcta gctaggccca agacctagtt acccagacag
 3300

tgagaagccc ctggaaggca gaaaagtgg gagcatggca gacaggaag ggaaacattt
 30 3360

tcagggaaaa gacatgtatc acatgtcttc agaagcaagt caggtttcat gtaaccgagt
 3420

35 gtcctcttgc gtgtccaaaa gtagccagg gctgtagcac aggcttcaca gtgattttgt
 3480

gttcagccgt gagtcacact acatgcccc gtgaagctgg gcattggtga cgtccagggt
 3540

40 gtccttgagt aataaaaaacg tatgttcctt aaaaaaaaaa aaa
 3583

45 <210> 32

<211> 905

<212> DNA

50 <213> Homo sapiens

55 <400> 32

caacacaggg gcagtctcca ggacctccac accattaaca agatgagcct tgtgctccct 60
 tgggctctag agaggaagcc cctctgagcc ctcagcccct ctttcctccc tctcctaaag
 5 120
 taatttgatc ctcaggaatt tgttctgccc tcattctggc ctggccagct ctgcatttga
 180
 10 caaatgccag gaagaggaaa ctgttgagaa aacggaacta ctggggaaaag ggagggtca
 240
 ctgagaacca tcccggtaac ccgaccgcg ctggtcacca tgaaccacat tgtgcaaacc
 300
 15 ttctctctg tcaacagcg ccagcctccc aactacgaga tgctcaagga ggagcaggaa
 360
 gtggctatgc tgggggggccc ccacaaccct gctccccga cgtccaccgt gatccacatc
 20 420
 cgcagcgaga cctccgtgcc tgaccatgtc gtctgggtccc tgttcaaac cctcttcatg
 480
 25 aacacctgct gcctgggctt catagcattc gcctactccg tgaagtctag ggacaggaag
 540
 atggttggcg acgtgaccgg ggcccaggcc tatgcctcca ccgccaagt cctgaacatc
 600
 30 tgggccctga ttttgggcat cttcatgacc attctgctcg tcattcatccc agtggttggtc
 660
 gtccaggccc agcgatagat caggaggcat cattgaggcc aggagctctg cccgtgacct
 720
 35 gtatcccacg tactctatct tccattcctc gccttgcccc cagaggccag gagctctgcc
 780
 cttgacctgt attccactta ctccaccttc cattcctcgc cctgtcccca cagccgagtc
 40 840
 ctgcatcagc cctttatcct cacacgcttt tctacaatgg cattcaataa agtgatatg
 900
 45 tttct
 905
 50 <210> 33
 <211> 782
 <212> DNA
 55 <213> Homo sapiens

5 <400> 33
 aggggcctta gcgtgccgca tcgccgagat ccagcgccca gagagacacc agagaaccca 60
 ccattggcccc ctttgagccc ctggcttctg gcatcctgtt gttgctgtgg ctgatagccc
 120
 10 ccagcagggc ctgcacctgt gtcccacccc acccacagac ggccttctgc aattccgacc
 180
 tcgtcatcag ggccaagttc gtggggacac cagaagtcaa ccagaccacc ttataccagc
 240
 15 gttatgagat caagatgacc aagatgtata aagggttcca agccttaggg gatgccgctg
 300
 20 acatccgggtt cgtctacacc cccgccatgg agagtgtctg cggatacttc cacagggtccc
 360
 acaaccgcag cgaggagttt ctcatgtctg gaaaactgca ggatggactc ttgcacatca
 420
 25 ctacctgcag tttcgtggct ccctggaaca gcctgagctt agctcagcgc cggggcttca
 480
 ccaagaccta cactgttggc tgtgaggaat gcacagtgtt tccctgttta tccatccctt
 540
 30 gcaaactgca gactggcact cattgcttgt ggacggacca gctcctccaa ggctctgaaa
 600
 agggcttcca gtcccgtcac cttgcctgcc tgccctggga gccagggctg tgcacctggc
 660
 35 agtccctgcg gtcccagata gcctgaatcc tgcccgaggt ggaactgaag cctgcacagt
 720
 40 gtccaccctg ttcccaactcc catctttctt ccggacaatg aaataaagag ttaccaccca
 780
 gc
 45 782

50 <210> 34
 <211> 1124
 <212> DNA
 <213> Homo sapiens
 55

<400> 34

5 gccgctgcca ccgcaccccg ccatggagcg gccgtcgctg cgcgccctgc tcctcggcgc 60
 cgctgggctg ctgctcctgc tcctgcccct ctcctcttcc tcctcttcgg acacctgcgg
 120
 10 cccctgcgag ccggcctcct gcccgccct gccccgctg ggctgcctgc tgggcgagac
 180
 ccgcgacgcg tgcggctgct gccctatgtg cggccgcggc gagggcgagc cgtgcggggg
 240
 15 tggcggcgcc ggccgggggt actgcgcgc gcccatggag tgcgtgaaga gccgcaagag
 300
 gcggaagggg aaagccgggg cagcagccgg cggccgggt gtaagcggcg tgtgcgtgtg
 360
 20 caagagccgc taccgggtgt gcggcagcga cggcaccacc taccgagcg gctgccagct
 420
 gcgcgccgcc agccagaggg ccgagagccg cggggagaag gccatcacc aggtcagcaa
 25 480
 gggcacctgc gagcaaggtc cttccatagt gacgcccccc aaggacatct ggaatgtcac
 540
 30 tgggtcccag gtgtacttga gctgtgaggt catcggaatc ccgacacctg tcctcatctg
 600
 gaacaaggta aaaaggggtc actatggagt tcaaaggaca gaactcctgc ctggtgaccg
 660
 35 ggacaacctg gccattcaga cccggggtgg ccagaaaag catgaagtaa ctggctgggt
 720
 gctggtatct cctctaagta aggaagatgc tggagaatat gaggccatg catccaattc
 40 780
 ccaaggacag gcttcagcat cagcaaaaat tacagtgggt gatgccttac atgaaatacc
 840
 45 agtgaaaaaa ggtgaagggt ccgagctata aacctccaga atattattag tctgcatggt
 900
 taaaagtagt catggataac tacattacct gttcttgct aataagtttc ttttaatcca
 960
 50 atccactaac actttagtta tattcactgg ttttacacag agaaatacaa aataaagatc
 1020
 acacatcaag actatctaca aaaatttatt atatatttac agaagaaaag catgcatatc
 1080
 55

attaaacaaa taaaatactt tttatcacaa aaaaaaaaaa aaaa
 1124

5

<210> 35

<211> 647

10

<212> DNA

<213> Homo sapiens

15

<400> 35

gctcactgag caccgtccca gcatccggac accacagcgg cccttcgctc cacgcagaaa 60
 20
 accacacttc tcataccttc actcaact tccttcccca aagccagaag atgcacaagg
 120
 aggaacatga ggtggctgtg ctgggggcac cccccagcac catccttcca aggtccaccg
 25
 tgattaacat ccacagcgag acctccgtgc ccgaccatgt cgtctgggtcc ctgttcaaca
 240
 ccctcttctt gaactgggtgc tgtctgggct tcatagcatt cgcctactcc gtaaagtcta
 30
 300
 gggacaggaa gatggttggc gacgtgaccg gggcccaggc ctatgcctcc accgccaagt
 360
 35
 gcctgaacat ctgggccctg attctgggca tcctcatgac cattggattc atcctgttac
 420
 tggatttcgg ctctgtaaca gtctaccata ttatgttaca gataatacag gaaaaacggg
 480
 40
 gttactagta gccgcccata gcttgaacc tttgcactcc actgtgcaat gctggccctg
 540
 45
 cacgctgggg ctgttgcccc tgcccccttg gtcttgcccc tagatacagc agtttatacc
 600
 cacacacctg tctacagtgt cattcaataa agtgcacgtg cttgtga
 647

50

<210> 36

<211> 5489

55

<212> DNA

<213> Homo sapiens

5

<400> 36

ggctgagttt tatgacgggc cgggtgctga agggcaggga acaacttgat ggtgctactt 60

10

tgaactgctt ttcttttctc ctttttgcac aaagagtctc atgtctgata tttagacatg
120atgagctttg tgcaaaaggg gagctggcta cttctcgctc tgcttcatcc cactattatt
180

15

ttggcacaac aggaagctgt tgaaggagga tgttcccatc ttggtcagtc ctatgcggat
240

20

agagatgtct ggaagccaga accatgccaa atatgtgtct gtgactcagg atccgttctc
300tgcatgaca taatatgtga cgatcaagaa ttagactgcc ccaaccaga aattccattt
360

25

ggagaatgtt gtgcagtttg cccacagcct ccaactgctc ctactcgccc tcctaattgt
420caaggacctc aaggcccaa gggagatcca ggccctcctg gtattcctgg gagaaatggt
480

30

gacctggta ttccaggaca accagggtcc cctggttctc ctggccccc tggaatctgt
540gaatcatgcc ctactggtcc tcagaactat tctcccagc atgattcata tgatgtcaag
600

35

tctggagtag cagtaggagg actgcaggc tatcctggac cagctggccc ccaggccct
660

40

ccgggtcccc ctggtacatc tggtcacccct gggtcccctg gatctccagg ataccaagga
720ccccctggtg aacctgggca agctggcctc tcaggccctc caggacctcc tggtgctata
780

45

ggtccatctg gtctgtctgg aaaagatgga gaatcaggta gaccgggacg acctggagag
840cgaggattgc ctggacctcc aggtatcaaa ggtccagctg ggatacctgg attccctggt
900

50

atgaaaggac acagaggctt cgatggacga aatggagaaa agggtgaaac aggtgctcct
960

55

ggattaaagg gtgaaaatgg tcttccaggc gaaaatggag ctctggacc catgggtcca
1020

agaggggctc ctggtgagcg aggacggcca ggacttcctg gggctgcagg tgctcggggc
 1080

5 . aatgacggtg ctcgaggcag tgatggtaa ccaggccctc ctggtcctcc tggaaactgcc
 1140

ggattccctg gatccctgg tgctaagggt gaagttggac ctgcagggtc tcctgggtca
 1200

10 aatggtgccc ctggacaaag aggagaacct ggacctcagg gacacgctgg tgctcaagg
 1260

cctcctggcc ctctgggat taatggtagt cctggtggtg aaggcgaaat gggctccgct
 1320

15 ggcattcctg gagctcctgg actgatggga gcccggggtc ctccaggacc agccgggtgt
 1380

20 aatggtgctc ctggactgag aggtgggtgca ggtgagcctg gtaagaatgg tgccaaagga
 1440

gagcccgagc cacgtggtga acgcggtgag gctggtattc cagggtgttc aggagctaaa
 1500

25 ggccaagatg gcaaggatgg atcacctgga gaacctggtg caaatgggct tccaggagct
 1560

gcaggagaaa ggggtgcccc tgggttcga ggacctgctg gaccaaattg catcccagga
 1620

30 gaaaagggtc ctgctggaga gcgtggtgct ccaggccctg caggggccag aggagctgct
 1680

35 ggagaacctg gcagagatgg cgtccctgga ggtccaggaa tgaggggcat gcccggaagt
 1740

ccaggaggac caggaagtga tgggaaacca gggcctccc gaagtcaagg agaaagtgg
 1800

40 cgaccaggct ctctgggcc atctggtccc cgaggtcagc ctggtgtcat gggcttccc
 1860

ggtcctaaag gaaatgatgg tgctcctggt aagaatggag aacgaggtgg ccctggagga
 1920

45 cctggccctc aggtcctcc tggaaagaat ggtgaaactg gacctcaagg accccaggg
 1980

cctactgggc ctggtggtga caaaggagac acaggacccc ctggtccaca aggattacaa
 2040

50 ggcttgctg gtacagggtg tcctccagga gaaaatggaa aacctgggga accagggtcca
 2100

55 aagggtgatg ccggtgcacc tggagctcca ggaggcaagg gtgatgctgg tgcccctggt
 2160

gaacgtggac ctccctggatt ggcagggggcc ccaggactta gaggtggagc tgggtccccct
 2220

5 ggtccccaag gaggaaggagg tgctgctggt cctcctgggc cacctggtgc tgctggtact
 2280

cctggtctgc aaggaatgcc tggagaaaga ggaggtcttg gaagtcctgg tccaaagggt
 2340

10 gacaagggtg aaccaggcgg ccaggtgct gatggtgtcc cagggaaaga tggcccaagg
 2400

15 ggtcctactg gtcctattgg tcctcctggc ccagctggcc agcctggaga taagggtgaa
 2460

ggtggtgccc ccggaattcc aggtatagct ggacctcgtg gtagccctgg tgagagaggt
 2520

20 gaaactggcc ctccaggacc tgctggtttc cctggtgctc ctggacagaa tggatgaacct
 2580

ggtggtgtaaag gagaaagagg ggctccgggt gagaaagggt aaggaggccc tcctggaggt
 2640

25 gcaggacccc ctggagggtc tggacctgct ggtcctcctg gtccccaagg tgtcaaagggt
 2700

gaacgtggca gtcctggtgg acctggtgct gctggtcttc ctggtgctcg tggctcttcct
 2760

30 ggtcctcctg gtagtaatgg taaccaggga ccccgaggtc ccagcggttc tccaggcaag
 2820

35 gatgggcccc caggtcctgc gggtaacact ggtgctcctg gcagccctgg agtgtctgga
 2880

ccaaaagggtg atgctggcca accaggagag aagggatcgc ctggtgcccc gggcccacca
 2940

40 ggagctccag gcccaattgg gattgctggg atcactggag cacggggtct tgaggacca
 3000

ccaggcatgc caggtcctag gggaaagccct ggccctcagg gtgtcaaggg tgaaagtggg
 3060

45 aaaccaggag ctaacggtct cagtggagaa cgtggtcccc ctggacccca gggctcttcct
 3120

50 ggtctggctg gtacagctgg tgaacctgga agagatggaa accctggatc agatggtctt
 3180

ccaggccgag atggatctcc tggtggaag ggtgatcgtg gtgaaaatgg ctctcctggt
 3240

55 gcccctggcg ctccctggtca tccaggccca cctggtcctg tcggtccagc tggaaagagt
 3300

ggtgacagag gagaagtg cctgctggc cctgctggtg ctcccgggcc tgctggttcc
 3360

5 cgaggtgctc ctggtcctca aggcccacgt ggtgacaaag gtgaaacagg tgaacgtgga
 3420

gctgctggca tcaaaggaca tcgaggattc cctggtaatc caggtgcccc aggttctcca
 3480

10 ggccctgctg gtcagcaggg tgcaatcgcc agtccaggac ctgcaggccc cagaggacct
 3540

gttggaccca gtggacctcc tggcaaagat ggaaccagtg gacatccagg tccattgga
 3600

15 ccaccagggc ctcgaggtaa cagaggtgaa agaggatctg agggctcccc aggccaccca
 3660

20 gggcaaccag gccctcctgg acctcctggt gccctgggc cttgctgtgg tgggtttgga
 3720

gccgctgcc a ttgctgggat tggaggtgaa aaagctggcg gttttgcccc gtattatgga
 3780

25 gatgaaccaa tggatttcaa aatcaacacc gatgagatta tgacttcact caagtctggt
 3840

aatggacaaa tagaaagcct cattagtcct gatggttctc gtaaaaaccc cgctagaaac
 3900

30 tgcaagagacc tgaatttctg ccacctgaa ctcaagagtg gagaatactg ggttgacctt
 3960

35 aaccaaggat gcaaatgga tgctatcaag gtattctgta atatggaaac tggggaaaca
 4020

tgcaatagt tcaatccttt gaattgtcca cggaaacact ggtggacaga ttctagtgt
 4080

40 gagaagaaac acgtttggtt tggagagtcc atggatggtg gttttcagtt tagctacggc
 4140

aatcctgaac ttctgaaga tgccttgat gtgcagctgg cattccttcg acttctctcc
 4200

45 agccgagctt ccagaaacat cacatatcac tgcaaaaata gcattgcata catggatcag
 4260

gccagtggaa atgtaaagaa ggccctgaag ctgatgggtt caaatgaagg tgaattcaag
 4320

gctgaaggaa atagcaaatt cacctacaca gttctggagg atggttgac gaaacacact
 4380

55 ggggaatgga gcaaaacagt ctttgaatat cgaacacgca aggtgtgag actacctatt
 4440

gtagatattg caccctatga cattggtggt cctgatcaag aatttggtgt ggacgttggc
 4500
 5 cctgtttgct ttttataaac caaactctat ctgaaatccc aacaaaaaaa atttaactcc
 4560
 atatgtgttc ctcttgttct aatcttgtca accagtgcaa gtgaccgaca aaattccagt
 4620
 10 tatttatttc caaaatgttt ggaaacagta taatttgaca aagaaaaatg atacttctct
 4680
 ttttttgctg ttccacaaaa tacaattcaa atgctttttg ttttattttt ttaccaattc
 4740
 15 caatttcaaa atgtctcaat ggtgctataa taaataaact tcaacactct ttatgataac
 4800
 20 aacactgtgt tatattcttt gaatcctagc ccatctgcag agcaatgact gtgctcacca
 4860
 gtaaaagata acctttcttt ctgaaatagt caaatacgaa attagaaaag cctccctat
 4920
 25 ttttaactacc tcaactggtc agaaacacag attgtattct atgagtccca gaagatgaaa
 4980
 aaaattttat acgttgataa aacttataaa tttcattgat taatctctctg gaagattggt
 5040
 30 ttaaaaagaa aagtgtaatg caagaattta aagaaatatt tttaaagcca caattatttt
 5100
 aatattggat atcaactgct tgtaaagggtg ctctcttttt ttcttgtcat tgctgggtcaa
 5160
 35 gattactaat atttggaag gctttaaaga cgcattgtat ggtgctaag tactttcact
 5220
 40 tttaaactct agatcagaat tggtgacttg cattcagaac ataatgcac aaaatctgta
 5280
 catgtctccc atcagaaaga ttcatggca tgccacaggg attctctctcc ttcatctgt
 5340
 45 aaagggtcaac aataaaaacc aaattatggg gctgcttttg tcacactagc atagagaatg
 5400
 50 tgttgaaatt taactttgta agcttgatg tggttggtga tctttttttt ccttacagac
 5460
 acccataata aaatatcata ttaaaattc
 5489

55

5

<210> 37

10 <211> 1722

<212> DNA

<213> Homo sapiens

15

<400> 37

20 ggggaaaaga gctaggaaaag agctgcaaag cagtgtgggc tttttccctt tttttgctcc 60

ttttcattac ccctcctccg ttttcaccct tctccggact tcgcgtagaa cctgcgaatt
12025 tcgaagagga ggtggcaaag tgggagaaaa gaggtgtag ggtttgggt tttttgttt
180ttgtttttgt tttttaattt cttgatttca acatttttct ccaccctctc ggctgcagcc
24030 aacgcctctt acctgttctg cggcgccgcg caccgctggc agctgagggt tagaaagcgg
300ggtgtatattt agattttaag caaaaatttt aaagataaat ccatttttct ctcccacccc
360

35

caacgccatc tccactgcat ccgatctcat tatttcggtg gttgcttggg ggtgaacaat
42040 tttgtggctt tttttccct ataattctga cccgctcagg cttgagggtt tctccggcct
480ccgctcactg cgtgcacctg gcgctgccct gcttccccc acctgttgca aggctttaat
54045 tcttgcaact gggacctgct cgcaggcacc ccagccctcc acctctctct acatttttgc
600aagtgtcttg gggagggcac ctgctctacc tgccagaaat tttaaaacaa aaacaaaaac
660

50

aaaaaaatct ccggggggccc tcttggtccc tttatccctg cactctcgct ctctgcccc
72055 accccgaggt aaagggggcg actaagagaa gatggtgttg ctcaccggcg tcctcctgct
780

gctggccgcc tatgcggggc cggcccagag cctgggctcc ttcgtgcact gcgagccctg
 840

5 cgacgagaaa gccctctcca tgtgcccccc cagccccctg ggctgcgagc tggtaagga
 900

gccgggctgc ggctgctgca tgacctgcgc cctggccgag gggcagtcgt gcggcgtcta
 960

10 caccgagcgc tgcgcccagg ggctgcgctg cctcccccg caggacgagg agaagccgct
 1020

gcacgccctg ctgcacggcc gcggggtttg cctcaacgaa aagagctacc gcgagcaagt
 1080

caagatcgag agagactccc gtgagcacga ggagcccacc acctctgaga tggccgagga
 1140

20 gacctactcc cccaagatct tccggcccaa acacaccgc atctccgagc tgaaggctga
 1200

agcagtgaag aaggaccgca gaaagaagct gaccagtc cagtttgcg ggggagccga
 1260

25 gaacactgcc ccccccgga tcatctctgc acctgagatg agacaggagt ctgagcaggg
 1320

cccctgccgc agacacatgg aggcttccct gcaggagctc aaagccagcc cagcatggt
 1380

30 gcccgtgct gtgtacctgc ccaattgtga ccgcaaagga ttctacaaga gaaagcagtg
 1440

caaaccttcc cgtggccgca agcgtggcat ctgctggtgc gtggacaagt acgggatgaa
 1500

gctgccaggc atggagtacg ttgacgggga ctttcagtgc cacaccttcg acagcagcaa
 1560

40 cgttgagtga tgcgtcccc cccaaccttt ccctcacc cccccccc cagccccgac
 1620

tccagccagc gcctccctcc accccaggac gccactcatt tcatctcatt taagggaana
 1680

45 atatatatct atctatttga ggaaaaaaaa aaaaaaaaaa aa
 1722

50 <210> 38

<211> 1200

55 <212> DNA

<213> Homo sapiens

5

<400> 38

aagatataaa agctccagaa acgttgactg ggaccactgg agacactgaa gaaggcaggg 60

10

gcccttagag tcttggttgc caaacagatt tgcagatcaa ggagaacca ggagtttcaa
120agaagcgcta gtaaggtctc tgagatcctt gcactagcta catcctcagg gtaggaggaa
180

15

gatggcttcc agaagcatgc ggctgctcct attgctgagc tgcctggcca aaacaggagt
240

20

cctgggtgat atcatcatga gaccagctg tgctcctgga tggttttacc acaagtocaa
300ttgctatggt tacttcagga agctgaggaa ctggtctgat gccgagctcg agtgtcagtc
360

25

ttacggaaac ggagcccacc tggcatctat cctgagttta aaggaagcca gcaccatagc
420agagtacata agtggctatc agagaagcca gccgatatgg attggcctgc acgaccacaa
480

30

gaagaggcag cagtggcagt ggattgatgg ggccatgtat ctgtacagat cctgggtctgg
540caagtccatg ggtgggaaca agcactgtgc tgagatgagc tccaataaca actttttaac
600

35

ttggagcagc aacgaatgca acaagcgcca acacttcctg tgcaagtacc gaccatagag
660caagaatcaa gattctgcta actcctgcac agccccgtcc tcttcctttc tgctagcctg
720

40

gctaaatctg ctcatatttt cagaggggaa acctagcaaa ctaagagtga taagggccct
780

45

actacactgg ctttttttagg cttagagaca gaaactttag cattggccca gtagtggctt
840ctagctctaa atgtttgccc cgccatccct ttccacagta tccttcttcc ctccctccct
900

50

gtctctggct gtctcgagca gtctagaaga gtgcatctcc agcctatgaa acagctgggt
960ctttggccat aagaagtaaa gatttgaaga cagaaggaag aaactcagga gtaagcttct
1020

55

agacccttc agcttctaca ccttctgcc ctctctccat tgctgcacc ccaccccagc
1080

5 cactcaactc ctgcttgttt ttcctttggc cataggaagg tttaccagta gaatccttgc
1140

taggttgatg tgggccatac attcctttaa taaaccattg tgtacataag aaaaaaaaaa
1200

10

15 <210> 39

<211> 1701

<212> DNA

20 <213> Homo sapiens

25 <400> 39

ccgcctccta gccgccgact cacacaaggc aggtgggtga ggaaatccag agttgccatg 60

gagaaaattc cagtgtcagc attcttgctc cttgtggccc tctctacac tctggccaga
120

30 gataccacag tcaaacctgg agccaaaaag gacacaaagg actctcgacc caaactgccc
180

cagaccctct ccagagggtg gggtgaccaa ctcatctgga ctacagata tgaagaagct
240

ctatataaat ccaagacaag caacaaaccc ttgatgatta ttcactcatt ggatgagtgc
300

40 ccacacagtc aagctttaaa gaaagtgttt gctgaaaata aagaaatcca gaaattggca
360

gagcagtttg tctcctcaa tctggtttat gaaacaactg acaaacacct ttctcctgat
420

45 ggccagtatg tccccaggat tatgtttgtt gacccatctc tgacagttag agccgatatc
480

actggaagat attcaaactg tctctatgct tacgaacctg cagatacagc tctgttgctt
540

50 gacaacatga agaaagctct caagttgctg aagactgaat tgtaaagaaa aaaaatctcc
600

55 aagcccttct gtctgtcagg ccttgagact tgaaaccaga agaagtgtga gaagactggc
660

tagtgtggaa gcatagtgaa cacactgatt aggttatggt ttaatgttac aacaactatt
720

5 ttttaagaaa aacaagtttt agaaatttgg tttcaagtgt acatgtgtga aaacaatatt
780

gtatactacc atagttagcc atgattttct aaaaaaaaaa ataatgttt tgggggtgtt
840

10 ctgttttctc caacttggtc tttcacagtg gttcgtttac caaataggat taaacacaca
900

caaatgctc aaggaaggga caagacaaaa ccaaaactag ttcaaatgat gaagacaaaa
15 960

gaccaagtta tcatctcacc acaccacagg ttctcactag atgactgtaa gtagacacga
1020

20 gcttaatcaa cagaagtatc aagccatgtg ctttagcata aaagaatatt tagaaaaaca
1080

tccaagaaa atcacatcac tacctagagt caactctggc caggaactct aaggtacaca
1140

25 ctttcattta gtaattaaat tttagtcaga ttttgcccaa cctaattgctc tcagggaag
1200

cctctggcaa gtagctttct ccttcagagg tctaatttag tagaaaggtc atccaaagaa
1260

30 catctgcact cctgaacaca ccctgaagaa atcctgggaa ttgacctgt aatcgatttg
1320

tctgtcaagg tcctaaagta ctggagtga ataaattcag ccaacatgtg actaattgga
35 1380

agaagagcaa aggggtgtga cgtgttgatg aggcagatgg agatcagagg ttactaggg
1440

40 ttaggaaacg tgaaaggctg tggcatcagg gtaggggagc attctgccta acagaaatta
1500

gaattgtgtg ttaatgtctt cactctatac ttaatctcac attcattaat atatggaatt
1560

45 cctctactgc ccagcccctc ctgatttctt tggcccctgg actatgggtgc tgtatataat
1620

gctttgcagt atctgttgct tgtcttgatt aacttttttg gataaaacct tttttgaaca
50 1680

gaaaaaaaa aaaaaaaaa a
1701

55

<210> 40

<211> 2259

<212> DNA

<213> Homo sapiens

<400> 40

cagttgcttc agcgtcccg tgtggctgtg ccgttggtcc tgtgcggtca cttagccaag 60

atgcctgagg aaaccagac ccaagaccaa ccgatggagg aggaggaggt tgagacgttc
120

gcctttcagg cagaaattgc ccagttgatg tcattgatca tcaatacttt ctactcgaac
180

aaagagatct ttctgagaga gctcatttca aattcatcag atgcattgga caaaatccgg
240

tatgaaagct tgacagatcc cagtaaatta gactctggga aagagctgca tattaacctt
300

ataccgaaca aacaagatcg aactctcact attgtggata ctggaattgg aatgaccaag
360

gctgacttga tcaataacct tgggtactatc gccaaagtctg ggaccaaagc gttcatggaa
420

gctttgcagg ctggtgcaga tatctctatg attggccagt tcggtgttgg tttttattct
480

gcttatttgg ttgctgagaa agtaactgtg atcaccaaac ataacgatga tgagcagtac
540

gcttgggagt cctcagcagg gggatcattc acagtgagga cagacacagg tgaacctatg
600

ggtcgtggaa caaaagttat cctacacctg aaagaagacc aaactgagta cttggaggaa
660

cgaagaataa aggagattgt gaagaaacat tctcagttta ttggatatcc cattactctt
720

tttgtggaga aggaacgtga taaagaagta agcgatgatg aggctgaaga aaaggaagac
780

aaagaagaag aaaaagaaaa agaagagaaa gagtcggaag acaaacctga aattgaagat
840

gttggttctg atgaggaaga agaaaagaag gatggtgaca agaagaaga gaagaagatt
900

aaggaaaagt acatcgatca agaagagctc aacaaaacaa agcccatctg gaccagaaat
 960
 5 cccgacgata ttactaatga ggagtacgga gaattctata agagcttgac caatgactgg
 1020
 gaagatcact tggcagtga gcatTTTTca gttgaaggac agttggaatt cagagccctt
 1080
 10 ctatttgtcc cagcagctgc tccttttgat ctgtttgaaa acagaaagaa aaagaacaac
 1140
 atcaaattgt atgtacgcag agttttcatc atggataact gtgaggagct aatccctgaa
 1200
 15 tatctgaact tcattagagg ggtggtagac tcggaggatc tccctctaaa catatcccgt
 1260
 gagatgttgc aacaaagcaa aattttgaaa gttatcagga agaatttggg caaaaaatgc
 1320
 20 ttagaactct ttactgaact ggcggaagat aaagagaact acaagaaatt ctatgagcag
 1380
 ttctctaaaa acataaagct tggaatacac gaagactctc aaaatcggaa gaagctttca
 1440
 gagctgttaa ggtactacac atctgcctct ggtgatgaga tggtttctct caaggactac
 1500
 30 tgcaccagaa tgaaggagaa ccagaaacat atctattata tcacaggatga gaccaaggac
 1560
 caggtagcta actcagcctt tgtggaacgt cttcggaaac atggcttaga agtgcattat
 1620
 35 atgattgagc ccattgatga gtactgtgtc caacagctga aggaatttga ggggaagact
 1680
 ttagtgtcag tcaccaaaga aggcctggaa cttccagagg atgaagaaga gaaaaagaag
 1740
 40 caggaagaga aaaaaacaaa gtttgagaac ctctgcaaaa tcatgaaaga catattggag
 1800
 45 aaaaaagtgtg aaaagggtgtg tgtgtcaaac cgattggtga catctccatg ctgtattgtc
 1860
 acaagcacat atggctggac agcaaacatg gagagaatca tgaaagctca agccctaaga
 1920
 50 gacaactcaa caatgggtta catggcagca aagaaacacc tggagataaa ccctgaccat
 1980
 tccattattg agaccttaag gcaaaaggca gaggctgata agaacgacaa gtctgtgaag
 2040

gatctggtca tcttgcttta tgaaactgcg ctctgtctt ctggcttcag tctggaagat
2100

5 cccagacac atgctaacag gatctacagg atgatcaaac ttggtctggg tattgatgaa
2160

gatgacccta ctgctgatga taccagtgtt gctgtaactg aagaaatgcc accccttgaa
2220

10 ggagatgacg acacatcacg catggaagaa gtagactaa
2259

15 <210> 41

<211> 7080

20 <212> DNA

<213> Homo sapiens

25 <400> 41

gagctagcgc tcaagcagag cccagcgcgg tgctatcgga cagagcctgg cgagcgcaag 60

30 cggcgcgggg agccagcggg gctgagcggg gccagggtct gaaccagat ttccagact
120

agctaccact ccgcttgccc acgccccggg agctcgcggc gcctggcggg cagcgaccag
180

35 acgtccgggg ccgctgcgct cctggccccg gaggcgtgac actgtctcgg ctacagaccc
240

agagggagca cactgccagg atgggagctg ctgggaggca ggacttcctc ttcaaggcca
300

40 tgctgaccat cagctggctc actctgacct gcttccctgg ggccacatcc acagtggctg
360

ctgggtgccc tgaccagagc cctgagttgc aaccctggaa ccctggccat gaccaagacc
45 420

accatgtgca tatcggccag ggcaagacac tgctgtcac ctcttctgcc acggtctatt
480

50 ccattccacat ctgagaggga ggcaagctgg tcattaaaga ccacgacgag ccgattgttt
540

tgcaaacccg gcacatcctg attgacaacg gaggagagct gcatgctggg agtgcctctt
600

55

gccctttcca gggcaatttc accatcattt tgtatggaag ggctgatgaa ggtattcagc
 660
 5 cggatcctta ctatggtctg aagtacattg gggttggtaa aggaggcgct cttgagttgc
 720
 atggacagaa aaagctctcc tggacatttc tgaacaagac ccttcaccca ggtggcatgg
 780
 10 cagaaggagg ctatTTTTTTT gaaaggagct ggggccaccg tggagttatt gttcatgtca
 840
 tcgaccccaa atcaggcaca gtcatccatt ctgaccggtt tgacacctat agatccaaga
 900
 15 aagagagtga acgtctggtc cagtatttga acgcggtgcc cgatggcagg atcctttctg
 960
 20 ttgcagtga tgaatgaagg tctcgaaatc tggatgacat ggccaggaag gcgatgacca
 1020
 aattgggaag caaacacttc ctgcaccttg gatttagaca cccttggagt tttctaactg
 1080
 25 tgaaggaaa tccatcatct tcagtgaag accatattga atatcatgga catcgaggct
 1140
 ctgctgctgc ccgggtattc aaattgttcc agacagagca tggcgaatat ttcaatgttt
 1200
 30 cttgtccag tgagtgggtt caagacgtgg agtggacgga gtgggttcgat catgataaag
 1260
 35 tatctcagac taaagggtgg gagaaaattt cagacctctg gaaagctcac ccaggaaaaa
 1320
 tatgcaatcg tccattgat atacaggcca ctacaatgga tggagttaac ctcagcacccg
 1380
 40 aggttgtcta caaaaaggc caggattata ggtttgcttg ctacgaccgg ggagagcct
 1440
 gccggagcta ccgtgtacgg ttcctctgtg ggaagcctgt gaggcccaaa ctcacagtca
 1500
 45 ccattgacac caatgtgaac agcaccattc tgaacttga ggataatgta cagtcatgga
 1560
 aacctggaga taccctggtc attgccagta ctgattactc catgtaccag gcagaagagt
 1620
 50 tccagggtgt tccctgcaga tcctgcgccc ccaaccaggc caaagtggca gggaaaccaa
 1680
 55 tgtacctgca catcggggag gagatagacg gcgtggacat gcgggcggag gttgggcttc
 1740

tgagccggaa catcatagtg atgggggaga tggaggacaa atgctacccc tacagaaacc
 1800

5 acatctgcaa tttctttgac ttcgatacct ttgggggcca catcaagttt gctctgggat
 1860

ttaaggcagc acacttggag ggacggagc tgaagcatat gggacagcag ctggtgggtc
 1920

10 agtaccgat tcaattccac ctggccggtg atgtagacga aaggggaggt tatgaccac
 1980

ccacatacat cagggacctc tccatccatc atacattctc tcgctgcgtc acagtccatg
 15 2040

gctccaatgg cttgttgatc aaggacgttg tgggctataa ctctttgggc cactgcttct
 2100

20 tcacggaaga tgggcccggag gaacgcaaca cttttgacca ctgtcttggc ctccctgtca
 2160

agtctggaac cctcctcccc tcggaccgtg acagcaagat gtgcaagatg atcacagagg
 2220

25 actcctaccc ggggtacatc cccaagccca ggcaagactg caatgctgtg tccaccttct
 2280

ggatggccaa tcccaacaac aacctcatca actgtgccgc tgcaggatct gaggaaactg
 30 2340

gattttggtt tatttttcac cacgtaccaa cgggcccctc cgtgggaatg tactccccag
 2400

35 gttattcaga gcacattcca ctgggaaaat tctataacaa ccgagcacat tccaactacc
 2460

gggctggcat gatcatagac aacggagtca aaaccaccga ggcctctgcc aaggacaagc
 2520

40 ggccgttcct ctcaatcatc tctgccagat acagccctca ccaggacgcc gaccgctga
 2580

agccccggga gccggccatc atcagacact tcattgccta caagaaccag gaccacgggg
 2640

45 cctggctgcg cggcggggat gtgtggctgg acagctgccg gtttctgac aatggcattg
 2700

gcctgaccct ggccagtggg ggaaccttcc cgtatgacga cggctccaag caagagataa
 50 2760

agaacagctt gtttggtggc gagagtggca acgtggggac ggaaatgatg gacaatagga
 2820

55 tctggggccc tggcggcttg gaccatagcg gaaggaccct ccctataggc cagaattttc
 2880

caattagagg aattcagtta tatgatggcc ccatcaacat ccaaaaactgc actttccgaa
 2940

5 agtttgtggc cctggagggc cggcacacca gcgccctggc cttccgcctg aataatgcct
 3000

ggcagagctg cccccataac aacgtgaccg gcattgcctt tgaggacgtt ccgattactt
 3060

10 ccagagtgtt cttcggagag cctggggcct ggttcaacca gctggacatg gatggggata
 3120

agacatctgt gttccatgac gtcgacggct ccgtgtccga gtaccctggc tcctacctca
 3180

15 cgaagaatga caactggctg gtccggcacc cagactgcat caatgttccc gactggagag
 3240

20 gggccatttg cagtgggtgc tatgcacaga tgtacattca agcctacaag accagtaacc
 3300

tgccaatgaa gatcatcaag aatgacttcc ccagccaccc totttacctg gagggggcgc
 3360

25 tcaccaggag caccattac cagcaatacc aaccggttgt caccctgcag aagggtaca
 3420

ccattccactg ggaccagacg gccccgcgcg aactcgccat ctggctcatc aacttcaaca
 3480

30 agggcgactg gatccgagtg gggctctgct acccgcgagg caccacattc tccatcctct
 3540

cgatgtttca caatgcctg ctgaagcaaa cgtccaagac gggcgtcttc gtgaggacct
 3600

tgcagatgga caaagtggag cagagctacc ctggcaggag ccactactac tgggacgagg
 3660

40 actcagggtt gttgttctg aagctgaaag ctcagaacga gagagagaag tttgctttct
 3720

gctccatgaa aggctgtgag aggataaaga ttaaagctct gattccaaag aacgcaggcg
 3780

45 tcagtgactg cacagccaca gcttaccaca agttcaccga gagggctgtc gtagacgtgc
 3840

cgatgcccaa gaagctcttt ggttctcagc tgaaaacaaa ggaccatttc ttggaggtga
 3900

50 agatggagag ttccaagcag cacttcttcc acctctggaa cgacttcgct tacattgaag
 3960

55 tggatgggaa gaagtacccc agttcggagg atggcatcca ggtggtggtg attgacggga
 4020

accaagggcg cgtggtgagc cacacgagct tcaggaactc cattctgcaa ggcataccat
 4080
 5 ggcagctttt caactatgtg gcgaccatcc ctgacaattc catagtgtt atggcatcaa
 4140
 agggaagata cgtctccaga ggcccatgga ccagagtgtt ggaaaagctt ggggcagaca
 4200
 10 ggggtctcaa gttgaaagag caaatggcat tcgttggtt caaaggcagc ttccggccca
 4260
 tctgggtgac actggacact gaggatcaca aagccaaaat cttccaagtt gtgcccattc
 4320
 15 ctgtggtgaa gaagaagaag ttgtgaggac agctgccgcc cgtgtccacc tcgtggtaga
 4380
 ctatgacggt gactcttggc agcagaccag tgggggatgg ctgggtcccc cagcccctgc
 4440
 cagcagctgc ctgggaaggc cgtgtttcag ccctgatggg ccaagggaag gctatcagag
 4500
 25 accctggtgc tgccacctgc ccctactcaa gtgtctacct ggagcccctg gggcggtgtc
 4560
 ggccaatgct ggaacattc actttcctgc agcctcttgg gtgcttctct cctatctgtg
 4620
 30 cctcttcagt gggggtttgg ggaccatctc aggagacctg ggtgtgtctg acagcaaaga
 4680
 tccactttgg caggagccct gaccagcta ggaggtagtc tggagggtctg gtcattcaca
 4740
 gatccccatg gtcttcagca gacaagttag ggtggtaaata gtaggagaaa gagccttggc
 4800
 40 cttaaggaaa tctttactcc tgtaagcaag agccaacctc acaggattag gagctggggt
 4860
 agaactggct atccttgggg aagaggcaag ccctgcctct ggccgtgtcc acctttcagg
 4920
 45 agactttgag tggcaggttt ggacttggac tagatgactc tcaaaggccc ttttagttct
 4980
 gagattccag aaatctgctg catttcacat ggtacctgga acccaacagt tcatggatat
 5040
 ccactgatat ccatgatgct gggtgcccca gcgcacacgg gatggagagg tgagaactaa
 5100
 55 tgcctagctt gaggggtctg cagtccagta gggcaggcag tcaggccat gtgcactgca
 5160

atgccagggtg gagaaatcac agagaggtaa aatggaggcc agtgccattt cagaggggag
 5220

5 gctcaggaag gcttcttgct tacaggaatg aaggctgggg gcattttgct ggggggagat
 5280

gaggcagcct ctggaatggc tcagggatcc agccctccct gccgctgcct gctgaagctg
 5340

10 gtgactacgg ggtcgccctt tgctcacgct tctctggccc actcatgatg gagaagtgtg
 5400

gtcagagggg agcaatgggc tttgctgctt atgagcacag aggaattcag tccccaggca
 15 5460

gccctgcctc tgactccaag aggggtgaagt ccacagaagt gagctcctgc cttagggcct
 5520

20 catttgctct tcatccaggg aactgagcac agggggcctc caggagaccc tagatgtgct
 5580

cgtactccct cggcctggga tttcagagct ggaaatatag aaaatatcta gcccaaagcc
 5640

25 ttcatTTTTaa cagatgggga aagtgagccc ccaagatggg aaagaaccac acagctaagg
 5700

gagggcctgg ggagccccac cctagccctt gctgccacac cacattgcct caacaaccgg
 5760

30 cccagagtg cccaggcact cctgaggtag cttctggaaa tggggacaag tcccctcgaa
 5820

ggaaaggaaa tgactagagt agaatgacag ctagcagatc tcttccctcc tgctcccage
 35 5880

gcacacaaac ccgccctccc cttggtgttg gcggtccctg tggccttcac tttgttact
 5940

40 acctgtcagc ccagcctggg tgcacagtag ctgcaactcc ccattggtgc tacctggctc
 6000

tcctgtctct gcagctctac aggtgaggcc cagcagaggg agtagggctc gccatgtttc
 6060

45 tggtagacca atttggtga tcttgggtgt ctgaacagct attgggtcca cccagtgccc
 6120

tttcagctgc tgcttaatgc cctgctctct ccttgggcca cttatagag agcccaaaga
 50 6180

gctcctgtaa gagggagAAC tctatctgtg gtttataatc ttgcacgagg caccagagtc
 6240

55 tccctgggtc ttgtgatgaa ctacatttat cccctttcct gccccaacca caaactcttt
 6300

ccttcaaaga gggcctgcct ggctccctcc acccaactgc acccatgaga ctcggtccaa
6360

5 gagtccattc cccaggtggg agccaactgt cagggaggtc tttccacca aacatctttc
6420

agctgctggg aggtgacat agggctctgc ttttaaagat atggctgctt caaaggccag
6480

10 agtcacagga aggacttctt ccaggagat tagtggatgat ggagaggaga gttaaaatga
6540

cctcatgtcc ttcttgcca cggttttgtt gaggtttcac tcttctaata caagggtctc
6600

15 aactgtgaa ccacttagga tgtgatcact ttcagggtggc caggaatgtt gaatgtcttt
6660

20 ggctcagttc atttaaaaaa gatatctatt tgaaagtctt cagagttgta catatgtttc
6720

acagtacagg atctgtacat aaaagtttct ttcctaaacc attcaccaag agccaatatc
6780

25 taggcatttt cttggtagca caaattttct tattgcttag aaaattgtcc tccttggtat
6840

ttctgtttgt aagacttaag tgagttaggc ctttaaggaa agcaacgctc ctctgaaatg
6900

30 cttgtctttt ttctgttgcc gaaatagctg gtcctttttc gggagttaga tgtatagagt
6960

35 gtttgtatgt aaacatttct tgtaggcatc accatgaaca aagatatatt ttctatttat
7020

ttattatatg tgcacttcaa gaagtcactg tcagagaaat aaagaattgt cttaaatgtc
7080

40

45

<210> 42

50 <211> 1973

<212> DNA

<213> Homo sapiens

55

<400> 42

5 gggatattgg agtagcaaga ggctgggaag ccatcactta ccttgactg agaaagaaga 60
 caaaggccag tatgcacagc tttcctccac tgctgctgct gctgttctgg ggtgtggtgt
 120
 10 ctcacagctt cccagcgact ctgaaacac aagagcaaga tgtggactta gtccagaaat
 180
 acctggaaaa atactacaac ctgaagaatg atgggaggca agttgaaaag cggagaaata
 240
 15 gtggcccagt ggttgaaaaa ttgaagcaaa tgcaggaatt ctttgggctg aaagtgactg
 300
 ggaaccaga tgctgaaacc ctgaaggtga tgaagcagcc cagatgtgga gtgcctgatg
 360
 20 tggctcagtt tgcctcact gaggggaacc ctgctggga gaaacacat ctgacctaca
 420
 ggattgaaaa ttacacgcca gatttgccaa gagcagatgt ggacctgcc attgagaaag
 480
 25 ccttccaact ctggagtaat gtcacacctc tgacattcac caaggtctct gagggtaag
 540
 cagacatcat gatattttt gtcaggggag atcatcgga caactctct tttgatggac
 600
 ctggaggaaa tcttgctcat gcttttaac caggcccagg tattggaggg gatgctcatt
 660
 35 ttgatgaaga tgaaaggtgg accaacaatt tcagagagta caattacat cgtgttgagg
 720
 ctcataaact cggccattct cttggactct ccattctac tgatatcggg gctttgatgt
 780
 40 accctagcta caccttcagt ggtgatgttc agctagctca ggatgacatt gatggcatcc
 840
 aagccatata tggacgttcc caaaatcctg tccagcccat cggcccacaa accccaaaag
 900
 45 cgtgtgacag taagctaacc tttgatgcta taactacgat tcggggagaa gtgatgttct
 960
 50 ttaaagacag attctacatg cgcacaaatc cttctaccc ggaagttgag ctcaatttca
 1020
 tttctgtttt ctggccacaa ctgccaatg ggcttgaagc tgcttacgaa tttgccgaca
 1080
 55

gagatgaagt ccggtttttc aaagggaata agtactgggc tggtcaggga cagaatgtgc
1140

5 tacacggata cccaaggac atctacagct cctttggctt ccctagaact gtgaagcata
1200

tcgatgctgc tctttctgag gaaaacactg gaaaaaccta cttctttggt gctaacaaat
1260

10 actggaggta tgatgaatat aaacgatcta tggatccagg ttatcccaaa atgatagcac
1320

atgactttcc tggaattggc cacaaagttg atgcagtttt catgaaagat ggatttttct
1380

15 atttctttca tggaacaaga caatacaaat ttgatcctaa aacgaagaga attttgactc
1440

20 tccagaaagc taatagctgg ttcaactgca ggaaaaattg aacattacta atttgaatgg
1500

aaaacacatg gtgtgagtcc aaagaagggt ttttcctgaa gaactgtcta ttttctcagt
1560

25 catttttaac ctctagagtc actgatacac agaataataat cttatttata cctcagtttg
1620

catatttttt tactatttag aatgtagccc tttttgtact gatataattt agttccacaa
1680

30 atggtgggta caaaaagtca agtttggtgc ttatggattc atataggcca gagttgcaaa
1740

gatcttttcc agagtatgca actctgacgt tgatcccaga gagcagcttc agtgacaaac
1800

35 atatcctttc aagacagaaa gagacaggag acatgagtct ttgccggagg aaaagcagct
1860

40 caagaacaca tgtgcagtca ctggtgtcac cctggatagg caagggataa ctcttctaac
1920

acaaaataag tgttttatgt ttggaataaa gtcaaccttg tttctactgt ttt
1973

45

<210> 43

50 <211> 1127

<212> DNA

<213> Homo sapiens

55

<400> 43

5 accaaatcaa ccataggtcc aagaacaatt gtctctggac ggcagctatg cgactcaccg 60
 tgctgtgtgc tgtgtgcctg ctgcctggca gcctggccct gccgctgcct caggaggcgg
 120
 10 gaggcattgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct
 180
 atgactcaga aacaaaaaat gccaacagtt tagaagccaa actcaaggag atgcaaaaat
 240
 15 tctttggcct acctataact ggaatgttaa actccgcgt catagaaata atgcagaagc
 300
 ccagatgtgg agtgccagat gttgcagaat actcactatt tccaaatagc ccaaaatgga
 360
 20 cttccaaagt ggtcacctac aggatcgtat catatactcg agacttaccg catattacag
 420
 tggatcgatt agtgtcaaag gctttaaaca tgtggggcaa agagatcccc ctgcatttca
 480
 25 ggaaagtgt atggggaact gctgacatca tgattggctt tgcgcgagga gctcatgggg
 540
 30 actcctaccc atttgatggg ccaggaaaca cgctggctca tgcctttgcg cctgggacag
 600
 gtctcgagg agatgctcac ttcgatgagg atgaacgctg gacggatggt agcagtctag
 660
 35 ggattaactt cctgtatgct gcaactcatg aacttggcca ttctttgggt atgggacatt
 720
 cctctgatcc taatgcagtg atgtatccaa cctatggaaa tggagatccc caaaatttta
 780
 40 aactttccca ggatgatatt aaaggcattc agaaactata tggaaagaga agtaattcaa
 840
 gaaagaaata gaaacttcag gcagaacatc cattcattca ttcattggat tgtatatcat
 900
 45 tgttgacaaa tcagaattga taagcactgt tcctccactc catttagcaa ttatgtcacc
 960
 50 cttttttatt gcagttgggt tttgaatgtc tttcactcct tttattgggt aaactccttt
 1020
 atggtgtgac tgtgtcttat tccatctatg agctttgtca gtgcgcgtag atgtcaataa
 1080
 55

atgttacata cacaataaa taaaatgttt attccatggt aaattta
1127

5

<210> 44

<211> 1163

10 <212> DNA

<213> Homo sapiens

15

<400> 44

agatccagca ggtgcgcgaa accgcggcgc gccgccctcc gccgttatat gaggccccgc 60

20 tccggcccca cgcggaaccc gcggctccga gccttcgccg gcgtcccgac ccgaggccgg
120

acccgaggcc agtcccgcgc ctgcgcagcc gaagccagtg cggggcctga gagggacgcg
180

25 cgccccgggg cccccgcgc gggcaccatg ggcgtgccc actccgcgtc tgaggaggtg
240

cgaggactcg agggcaagac cggcttctca tcggatcaga tcgagcagct ccatcggaga
300

30 tttaagcagc tgagtggaga tcagcctacc attcgcaagg agaactcaa caatgtcccg
360

35 gacctggagc tcaaccccat ccgatccaaa attgttcgtg ccttcttcga caacaggaac
420

ctgcgcaagg gaccagtg gctggctgat gagatcaatt tcgaggactt cctgaccatc
480

40 atgtcctact tccggcccat cgacaccacc atggacgagg aacaggtgga gctgtcccg
540

aaggagaagc tgagatttct gttccacatg tacgactcgg acagcgacgg ccgcatcact
45 600

ctggaagaat atcgaaatgt aaagtggctg aggagctgct gtcgggaaac cctcacatct
660

50 agaaggagtc cgctcgctcc atcgccgacg gggccatgat ggaggcggcc agcgtgtgca
720

tggggcagat ggagcctgat caggtgtacg aggggatcac cttcgaggac ttcctgaaga
780

55

tctggcaggg gatcgacatt gagaccaaga tgcacgtccg ctctcttaac atggaaacca
 840

5 tggccctctg cactgaccc accgccacct ccgcggagag actgcacttt gcaatggggc
 900

cgctccccg cgtagctgga gcagcccagg cccggcggac agcctcttcc tgcagcgccg
 960

10 gtacatagcc aaggctcgtc tgcgcacctt gtgtcttgta gggatatgga tgtgggactt
 1020

15 cgctgttttt atctccaata aaaaaaaaaa aaaaagggtt gttaattaaa aaaaaaaaaa
 1080

aaaagaaaaa aaaaaaaaaa aaaaaaaaaa aaaaagaaaa aaaaaaaaaa aaaaaaaaaa
 1140

20 aaaaaaaaaa aaaaaaaaaa aaa
 1163

25 <210> 45
 <211> 2007
 <212> DNA

30 <213> Homo sapiens

35 <400> 45
 agcggagggg gaaatcctga gcgcaggcca gggttgtttg gttttgaggt gtgctgggat 60
 gaaaggcacc ctggaagtgg aaggtaaag agcaatggaa aaacttcacg gcaagattag
 120

40 aaagatacct gagcccaata ccgcctgat gtcgtgggcc acacctccgg gttaccaggg
 180

45 gaagggagga agcaaaactgt catattgatg tggctctaaa caacaacagt gtgcgaaggc
 240

ccaggggcac tttgggattg accaagagga aacacaagtt gcacaatgat acaatcttgt
 300

50 tgggtacaatt gtcagagaag ggaactocca cagcaaaggc cataaaacca tccagggcag
 360

tctggggcgg ctcagttctg cggtgccagg gaggggagca gagctcagcc ccgtcccaaa
 420

55

cacagatggg accatgaa^{ct} ccggacacag cttcagccag accccctcgg cctccttcca
 480

5 tggcgccgga ggtggctggg gccggcccag gagcttcccc agggctccca ccgtccatgg
 540

cggtgcgggg ggagcccga tctccctgtc cttcaccacg cggagctgcc cacc^{cc}cctgg
 600

10 agggctcttg ggttctggaa gaagcagccc cctactaggc ggaaatggga aggccacat
 660

gcagaatctc aacgaccgcc tggcctccta cgtggagaag gttcgcgcc tggaggaggc
 15 720

caacatgaag ctggaaagcc gcatcctgaa atggcaccag cagagagatc ctggcagtaa
 780

20 gaaagattat tcacagtatg aggaaaacat cacacac^{ct}g caggagcaga tagtggatgg
 840

taagatgacc aatgctcaga ttattcttct cattgacaat gccaggatgg cagtggatga
 900

25 cttcaacctc aagtatgaaa atgaacactc ctttaagaaa gacttggaaa ttgaagtoga
 960

gggcctccga aggaccttag acaacctgac cattgtcaca acagacctag aacaggaggt
 30 1020

ggaaggaatg aggaaagagc tcattctcat gaagaagcac catgagcagg aaatggagaa
 1080

35 gcatcatgtg ccaagtgact tcaatgtcaa tgtgaagg^{tg} gatacgggtc ccaggaaga
 1140

tctgattaag gtcctggagg atatgagaca aga^{at}atgag cttataataa agaagaagca
 1200

40 tcgagacttg gacacttgg^t ataaagaaca gtctgcagcc atgtcccagg aggcagccag
 1260

tccagccact gtgcagagca gacaagg^{tga} catccacgaa ctgaagcgca cattccaggc
 1320

45 cctggagatt gacctgcaga cacagtacag cacgaaatct gctttggaaa acatgttatc
 1380

cgagacc^{cag} tctcgg^{tact} cctgcaagct ccaggacatg caagagatca tctcc^{acta}
 50 1440

tgaggaggaa ctgacgcagc tacgccatga actggagcgg cagaacaatg aataccaagt
 1500

55 gctgctgggc atcaaaa^{ccc} acctggagaa ggaaatcacc acgtaccgac ggctcctgga
 1560

EP 1 439 393 A2

gggagagagt gaaggacac gggaagaatc aaagtcgagc atgaaagtgt ttgcaactcc
 1620
 5 aaagatcaag gccataacc aggagaccat caacggaaga ttagttcttt gtcaagtga
 1680
 tgaaatccaa aagcacgcat gagaccaatg aaagtttccg cctgttgtaa aatctatatt
 1740
 10 cccccaagga aagtccttgc acagacacca gtgagtgagt tctaaaagat acccttgga
 1800
 ttatcagact cagaaacttt tatttttttt ttctgtaact gtctcaccag acttctcata
 1860
 15 atgctcttaa tatattgcac ttttctaatac aaagtgcgag tttatgaggg taaagtctta
 1920
 20 ctttcctact gcagccttca gattctcatc attttgcac tattttgtag ccaataaaac
 1980
 tccgcactag caaaaaaaaa aaaaaa
 2007
 25
 <210> 46
 30 <211> 1650
 <212> DNA
 <213> Homo sapiens
 35
 <400> 46
 40 gccttttttg cagtctcagg acgggcgctt tggagccggc cccaggcagc gtgtgtcggg 60
 cgctagtctt ggagaactag tcctcgactc acggtgaggg aatggaccga cacgggtatt
 120
 45 gtaccgctga gggaaaggag cgggactccg gacctccagg agtgcaagga tgatgctgaa
 180
 aggaataaca aggccttatct ctaggatcca taagttggac cctgggcggt ttttacacat
 240
 50 ggggaccag gctcgccaaa gcattgctgc tcacctagat aaccagggtc cagttgagag
 300
 tccgagagct atttcccga ccaatgagaa tgaccgggcc aagcatgggg atcagcacga
 360
 55

gggtcagcac tacaacatct cccccagga tttggagact gtatttcccc atggccttcc
 420

5 tcctcgcttt gtgatgcagg tgaagacatt cagtgaagct tgcctgatgg taaggaaacc
 480

agccctagaa cttctgcatt acctgaaaaa caccagtttt gcttatccag ctatacgata
 540

10 tcttctgtat ggagagaagg gaacaggaaa aaccctaagt ctttgccatg ttattcattt
 600

ctgtgcaaaa caggactggc tgatactaca tattccagat gtcacatctt gggtgaaaaa
 15 660

ttgtcgggat cttctgcagt ccagctacaa caaacagcgc tttgatcaac ctttagaggc
 720

20 ttcaacctgg ctgaagaatt tcaaaactac aaatgagcgc ttcctgaacc agataaaagt
 780

tcaagagaag tatgtctgga ataagagaga aagcactgag aaagggagtc ctctgggaga
 840

25 agtggttgaa cagggcataa cacgggtgag gaacgccaca gatgcagttg gaattgtgct
 900

gaaagagcta aagaggcaaa gttctttggg tatgtttcac ctccatagtg ccgtggatgg
 30 960

aatcaatgct ctttggggaa gaaccactct gaaaagagaa gataaaagcc cgattgcccc
 1020

35 cgaggaatta gcacttggtc acaacttgag gaaaatgatg aaaaatgatt ggcatggagg
 1080

cgccattgtg tcggctttga gccagactgg gtctctcttt aagccccgga aagcctatct
 1140

40 gccccaggag ttgctgggaa aggaaggatt tgatgccctg gatcccttta ttcccatcct
 1200

ggtttccaac tataacccaa aggaatttga aagttgtatt cagtattatt tggaaaacaa
 1260

45 ttggcttcaa catgagaaag ctctacaga agaagggaaa aaagagctgc tgttcctaag
 1320

taacgcgaac ccctcgctgc tggagcggca ctgtgcctac ctctaagcca agatcacagc
 50 1380

atgtgaggaa gacagtggac atctgcttta tgctggaccc agtaagatga ggaagtcggg
 1440

55 cagtacacag gaagaggagc caggcccttg tacctatggg attggacagg actgcagttg
 1500

gctctggacc tgcattaaaa tgggtttcac tgtgaatgcg tgacaataag atattccctt
1560

5 gttcctaaaa ctttatatca gtttattgga tgtgggtttt cacatttaag ataattatgg
1620

ctcttttcct aaaaaataaa atatctttct
1650

10

<210> 47

15 <211> 2566

<212> DNA

<213> Homo sapiens

20

<400> 47

25 cgcttttttt ttttttttct ttttttgaga tggagcttgc tctgtcacc aggctggagt 60

gcagtggcac gatcacagct cactgcaact tccgccacct gggttcaagc aattttcctg
120

30 cttcaacctc ccgagtagtt gagattacag gcacgtgcc cccacacctga ctgatttttg
180

tatttttagt agagacaggg ttccaccatg ttggccaggc tggctctgaa ctctgacct
240

35 caagtgatcc acccacctca gtctaccaa gtgctgggat tacaggttgt gagccactgc
300

acccggcctc tgtctgaact ttaaatgatg gagtatccca gaggtcaggc tttagagctc
360

40 ttctttcttc catctacaga gtgctcattt ctttggtgat ctcatcagc ctcacggctt
420

tgaatgttat atgctgataa gtcccaactt tctctgtct gcctaaactt cccctaatag
480

cagaacctga tatcaaagtg cctatttgac atctccactt agatatctaa taagcatctt
540

50 taatgtaaaa tttccaaaac tgagctccta caattccctc ccacacttgt tcagttttcc
600

ccatctaagc taatggcaac tccatccctc cagttgcttt ggccaaaact tttgagttgt
660

55

ctttgactgc tttttttctc ccttcttaca ttgtgctcat cctttctttc aggcaaattc
 720
 5 tgtttggtat accttcaa atactagaa ttctatactt ctactaccc ctcatccca
 780
 ttatctttga aacacactcc aatgaggttt ttacccccac tattccacca aaaacactct
 840
 10 tgtgaaagtc accagatgat ggttcttcag gctatcatct gtctcctgaa ttattttaag
 900
 agcctcccta actggtctcc ttgttcacgc cctgctccc ttactctat tctcaatata
 960
 15 acagtcagag ggatcttata aaaccgtaag tcagatcata taattctgtg tgaaaccctc
 1020
 caatggtatc ccacttcaga gtaaaagtta aagggtttat ttgatctct aaatattttg
 1080
 atccctatga tctagtctct tcttaccbaa agtatgggcc tcataccagc agaactggca
 1140
 25 ttctctggga gcttggtaga aatgtagaat ctctggctct aagattttct aaatcagaat
 1200
 ctgcattttc atcagctctc ttggcaattc atatgtttga gaaggactga tgtagtctc
 1260
 30 tactgcctct cctgctgcta tgtgctgctc tagtcacact gtctcctgg ctatttcgat
 1320
 aagatggaaa ctctcctgcc tcagggtttt tgcacctact gctccctctg tctaggataa
 1380
 tcttccccag aaaactgcat gccagttgcc ttatttcctt cagggtctta ttgaagtca
 1440
 40 tttctcatta aacactttct ggccatcct gtctaaaact gcatcccca acccttcta
 1500
 tcccttttct ccactttttt ctttttttaa actatagttc ttatcaacat agtatatgtt
 1560
 45 ttgcttattt atcctgttta ttgtctgact caacaagtat aatttgacaa agaaaaatga
 1620
 tacttctctt ttttgctgt tccaccaa atcaattcaa tgctttttgt tttattttt
 1680
 50 taccaattcc aatttcaaaa tgtctcaatg gtgctataat aaataaactt caacactctt
 1740
 tatgataaca aactgtgtt atattctttg aatcctagcc catctgcaga gcaatgactg
 1800

tgctcaccag taaaagataa cctttctttc tgaaatagtc aaatacgaaa ttagaaaagc
 1860
 5 cctccctatt ttaactacct caactgggtca gaaacacaga ttgtattcta tgagtcccag
 1920
 aagatgaaaa aaattttata cgttgataaa acttataaat ttcattgatt aatctcctgg
 1980
 10 aagattgggt taaaaagaaa agtgtaatgc aagaatttaa agaaatattt ttaaagccac
 2040
 aattatttta atattggata tcaactgctt gttaaagggtc tcctcctttt tcttgtcatt
 2100
 15 gctgggtcaag attactaata tttgggaagg ctttaaagac gcatgttatg gtgctaattg
 2160
 20 actttcactt ttaactctta gatcagaatt gttgacttgc attcagaaca taaatgcaca
 2220
 aaatctgtac atgtctccca tcagaaagat tcattggcat gccacagggg attctcctcc
 2280
 25 ttcacacctgt aaagggtcaac aataaaaacc aaattatggg gctgcttttg tcacactagc
 2340
 atagagaatg tgttgaaatt taactttgta agcttgatg tggttgttga tctttttttt
 2400
 30 ccttacagac acccataata aaatatcata ttaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
 2460
 35 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
 2520
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa
 2566
 40
 <210> 48
 <211> 2067
 45 <212> DNA
 <213> Homo sapiens
 50
 <400> 48
 cgcttttttt tttttttttt atgaataaat tgtatgtgtt tctagctgaa actactcacc 60
 55

aatatgcatg ttaaattcaa tcctctctta cctattcttt gatataactc cttgaagttt.
120

5 tcccatcttc ctacatcatc tccccacccc ccaactgagtc atttctataa tacaacata
180

ttatcttttt attaaattaa aaatctacct gtacaccttg aatgacaatg ctcggagctc
240

10 ccctgtggtc atcgacgcct ccaactgccat tgatgcacca tccaacctgc gtttcctggc
300

caccacccc aattccttgc tggatatcatg gcagccgcc cgtgccagga ttaccggcta
15 360

catcatcaag tatgagaagc ctgggtctcc tcccagagaa gtggccctc ggccccgcc
420

20 tgggtgcaca gaggctacta ttactggcct ggaaccggga accgaatata caatttatgt
480

cattgccctg aagaataatc agaagagcga gccctgatt ggaaggaaaa agacaggaca
540

25 agaagctctc tctcagacaa ccatctcatg ggccccattc caggacactt ctgagtacat
600

catttcatgt catcctgttg gcactgatga agaaccctta cagttcaggg ttcttggaac
30 660

ttctaccagt gccactctga caggcctcac cagaggtgcc acctacaaca tcatagtgga
720

35 ggcactgaaa gaccagcaga ggcataaggt tcgggaagag gttgttaccg tgggcaactc
780

tgtcaacgaa ggcttgaacc aacctacgga tgactcgtgc tttgaccct acacagtttc
840

40 ccattatgcc gttggagatg agtgggaacg aatgtctgaa tcaggcttta aactgttgtg
900

ccagtgttta ggctttggaa gtggtcattt cagatgtgat tcatctagat ggtgccatga
45 960

caatgggtgtg aactacaaga ttggagagaa gtgggaccgt caggagaaa atggccagat
1020

50 gatgagctgc acatgtcttg ggaacgaaa aggagaattc aagtgtgacc ctcatgaggc
1080

aacgtgttat gatgatgga agacatacca cgtaggagaa cagtggcaga aggaatatct
1140

55 cgggtgccatt tgctcctgca catgctttgg aggccagcgg ggctggcgct gtgacaactg
1200

ccgcagacct gggggtgaac ccagtcgccga aggcactact ggccagtcct acáaccagta
1260

5 ttctcagaga taccatcaga gaacaaacac taatgttaat tgcccaattg agtgcttcat
1320

gccttttagat gtacaggctg acagagaaga ttcccagagag taaatcatct ttccaatcca
1380

10 gaggaacaag catgtctctc tgccaagatc catctaaact ggagtgatgt tagcagaccc
1440

agcttagagt tcttctttct ttcttaagcc ctttgctctg gaggaagttc tccagcttca
1500

15 gctcaactca cagcttctcc aagcatcacc ctgggagttt cctgagggtt ttctcataaa
1560

20 tgagggtctg acattgcctg ttctgcttcg aagtattcaa taccgctcag tattttaaat
1620

gaagtgattc taagatttgg tttgggatca ataggaaagc atatgcagcc aaccaagatg
1680

25 caaatgtttt gaaatgatat gacccaaatt ttaagtagga aagtcaccca aacacttctg
1740

ctttcactta agtgtctggc ccgcaatact gtaggaacaa gcatgatctt gttactgtga
1800

30 tattttaaat atccacagta ctcacttttt ccaaagatc ctagtaattg cctagaaata
1860

35 tctttctctt acctgttatt tatcaatttt tcccagtatt ttatcacgga aaaaattgta
1920

ttgaaaacac ttagtatgca gttgataaga ggaatttggg ataattatgg tgggtgatta
1980

40 ttttttatac tgtatgtgcc aaagctttac tactgtggaa agacaactgt ttttaataaaa
2040

gatttacatt ccaaaaaaaaa aaaaaaa
2067

45

<210> 49

50 <211> 1752

<212> DNA

55 <213> Homo sapiens

<400> 49

5 ctgctccttc taggatctcc gcctggttcg gccgcctgc ctccactcct gcctccacca 60
 tgtccatcag ggtgaccag aagtcctaca aggtgtccac ctctggcccc cgggccttca
 120

10 gcagccgctc ctacacgagt gggcccgggt cccgcatcag ctctctgagc ttctcccag
 180

tgggcagcag caactttcgc ggtggcctgg gcggcggcta tggtagggcc agcggcatgg
 240

15 gaggcacac cgcagttacg gtcaaccaga gcctgctgag ccccttctgc ctggaggtgg
 300

acccaacat ccaggccgtg cgcaccagc agaaggagca gatcaagacc ctcaacaaca
 360

20 agtttgctc cttcatagac aaggtagcgt tcctggagca gcagaacaag atgctggaga
 420

ccaagtggag cctcctgcag cagcagaaga cggctcgaag caacatggac aacatgttcg
 480

25 agagctacat caacaacctt aggcggcagc tggagactct gggccaggag aagctgaagc
 540

30 tggaggcgga gcttggaac atgcaggggc tggtaggaga cttcaagaac aagtatgagg
 600

atgagatcaa taagcgtaca gagatggaga acgaatttgt cctcatcaag aaggatgtgg
 660

35 atgaagctta catgaacaag gtagagctgg agtctgcct ggaagggtg accgacgaga
 720

tcaacttcct caggcagcta tatgaagagg agatccggga gctgcagtcc cagatctcgg
 780

40 acacatctgt ggtgctgtcc atggacaaca gccgctccct ggacatggac agcatcattg
 840

45 ctgaggtcaa ggcacagtac gaggatattg ccaaccgcag ccgggctgag gctgagagca
 900

tgtaccagat caagtatgag gagctgcaga gcctggctgg gaagcacggg gatgacctgc
 960

50 ggcgcaaaa gactgagatc tctgagatga accggaacat cagccggctc caggctgaga
 1020

ttgagggcct caaaggccag agggcttccc tggaggccgc cattgcagat gccgagcagc
 1080

55

gtggagagct ggccattaag gatgccaacg ccaagttgtc cgagctggag gccgccctgc
1140

5 agcggggccaa gcaggacatg gcgcggcagc tgcgtgagta ccaggagctg atgaacgtca
1200

agctggccct ggacatcgag atcgccacct acaggaagct gctggagggc gaggagagcc
1260

10 ggctggagtc tgggatgcag aacatgagta ttcatacgaa gaccaccagc ggctatgcag
1320

gtggtctgag ctccgacctat gggggcctca caagccccgg cctcagctac agcctgggct
1380

ccagcttttg ctctggcgcg ggctccagct ccttcagccg caccagctcc tccagggccg
1440

20 tggttgtgaa gaagatcgag acacgtgatg ggaagctggg gtctgagtcc tctgacgtcc
1500

tgcccaagtg aacagctgcg gcagcccctc ccagcctacc cctcctgcgc tgccccagag
1560

25 cctgggaagg aggccgctat gcagggtagc actgggaaca ggagaccac ctgaggctca
1620

gccctagccc tcagcccacc tggggagttt actacctggg gacccccctt gcccatgcct
1680

30 ccagctacaa aacaattcaa ttgctttttt tttttgtcc aaaataaaac ctcagctagc
1740

35 tctgccaac cc
1752

40 <210> 50

<211> 1412

<212> DNA

45 <213> Homo sapiens

<400> 50

50 cggggtcgtc cgcaaagcct gagtccgtc cttctctct ccccgacag catgagcttc 60

accactcgtc ccaccttctc caccaactac cggtccttg gctctgtcca ggcgcccagc
120

55

taaggcgccc ggccggtcag cagcgcgccc agcgtctatg caggcgctgg gggctctggt
 180
 5 tcccggtatct ccgtgtcccg ctccaccagc ttcaggggcg gcatggggtc cgggggcctg
 240
 gccaccggga tagccggggg tctggcagga atgggaggca tccagaacga gaaggagacc
 300
 10 atgcaaagcc tgaacgaccg cctggcctct tacctggaca gagtgaggag cctggagacc
 360
 15 gagaaccgga ggctggagag caaaatccgg gagcacttgg agaagaaggg accccaggtc
 420
 agagactgga gccattactt caagatcatc gaggacctga gggctcagat cttcgcaaatt
 480
 20 actgtggaca atgcccgcat cgttctgcag attgacaatg cccgtcttgc tgctgatgac
 540
 tttagagtca agtatgagac agagctggcc atgcgccagt ctgtggagaa cgacatccat
 600
 25 gggctccgca aggtcattga tgacaccaat atcacacgac tgcagctgga gacagagatc
 660
 gaggtctctca aggaggagct gctcttcatg aagaagaacc acgaagagga agtaaaaggc
 720
 30 ctacaagccc agattgccag ctctgggttg accgtggagg tagatgcccc caaatctcag
 780
 35 gacctcgcca agatcatggc agacatccgg gcccaatatg acgagctggc tcggaagaac
 840
 cgagaggagc tagacaagta ctgggtctcag cagattgagg agagcaccac agtggtcacc
 900
 40 acacagtctg ctgagggttg agctgctgag acgacgctca cagagctgag acgtacagtc
 960
 cagtccttgg agatcgacct ggactccatg agaaatctga aggccagctt ggagaacagc
 1020
 45 ctgagggagg tggaggcccg ctacgcocta cagatggagc agctcaacgg gatcctgctg
 1080
 caccttgagt cagagctggc acagaccgg gcagagggac agcgccaggc ccaggagtat
 1140
 50 gaggccctgc tgaacatcaa ggtcaagctg gaggtgaga tcgccaccta ccgccgcctg
 1200
 55 ctggaagatg gcgaggactt taatcttggg gatgccttgg acagcagcaa ctccatgcaa
 1260

accatccaaa agaccaccac ccgccggata gtggatggca aagtgggtgc tgagaccaat
 1320
 5 gacaccaaag ttctgaggca ttaagccagc agaagcaggg taccctttgg ggagcaggag
 1380
 gccataaaaa agttcagagt tcattggatg tc
 1412
 10
 <210> 51
 15 <211> 1407
 <212> DNA
 <213> Homo sapiens
 20
 <400> 51
 25 cgcgaaatcgc agcttctgag accaggggtg ctccgtccgt gctccgcctc gccatgactt 60
 cctacagcta tcgccagtcg tcggccacgt cgtccttcgg aggcctgggc ggcggtccg
 120
 30 tgcgttttgg gccgggggtc gccttttcgg cgcccagcat tcacgggggc tccggcgggc
 180
 gcggcgatc cgtgtcctcc gcccgctttg tgtcctcgtc ctctcgggg gcctacggcg
 240
 35 gcggctacgg cggcgctcctg accgcgtccg acgggctgct ggccgggcaac gagaagctaa
 300
 ccatgcagaa cctcaacgac cgcttggcct cctacctgga caaggtgcgc gccctggagg
 360
 40 cggccaacgg cgagctagag gtgaagatcc gcgactggta ccagaagcag gggcctgggc
 420
 cctcccgcga ctacagccac tactacagca ccatccagga cctgcgggac aagattcttg
 480
 gtgccaccat tgagaactcc aggattgtcc tgcagatcga caatgcccg ctggctgcag
 540
 50 atgacttccg aaccaagttt gagacggaac aggcctctgc catgagcgtg gaggccgaca
 600
 tcaacggcct gcgcaggtg ctggatgagc tgaccctggc caggaccgac ctggagatgc
 660
 55

agatcgaagg cctgaaggaa gagctggcct acctgaagaa gaaccatgag gaggaaatca
 720
 5 gtacgctgag gggccaagtg ggaggccagg tcagtgtgga ggtggattcc gctccgggca
 780
 ccgatctcgc caagatcctg agtgacatgc gaagccaata tgaggatcatg gccgagcaga
 840
 10 accggaagga tgctgaagcc tggttcacca gccggactga agaattgaac cgggaggtcg
 900
 ctggccacac ggagcagctc cagatgagca ggtccgaggt tactgacctg cggcgacccc
 15 960
 ttcagggctc tgagattgag ctgcagtcac agctgagcat gaaagctgcc ttggaagaca
 1020
 20 cactggcaga aacggaggcg cgctttggag ccagctggc gcatatccag gcgctgatca
 1080
 gcggtattga agcccagctg ggcgatgtgc gagctgatag tgagcggcag aatcaggagt
 1140
 25 accagcggct catggacatc aagtcgcggc tggagcagga gattgccacc taccgcagcc
 1200
 tgctcgaggg acaggaagat cactacaaca atttgtctgc ctccaaggtc ctctgaggca
 1260
 30 gcaggctctg gggcttctgc tgccttttg aggtgtctt ctgggtagag ggatgggaag
 1320
 gaagggaccc ttacccccgg ctcttctct gacctgcaa taaaaattta tggccaagg
 35 1380
 gaaaaaaaa aaaaaaaaa aaaaaaa
 1407
 40
 <210> 52
 <211> 1723
 45 <212> DNA
 <213> Homo sapiens
 50
 <400> 52
 caaccatcct gaagctacag gtgctccctc ctggaatctc caatggattt cagtcgcaga 60
 55

agcttccaca gaagcctgag ctctccttg caggccccctg tagtcagtac agtgggcatg
 120
 5 cagcgccctcg ggacgacacc cagcgtttat gggggtgctg gaggccgggg catccgcatc
 180
~~tccaactcca gatcacctgt gaactatggg agcgatetea eaggcggcgg~~ ggacctgttt
 240
 10 gttggcaatg agaaaatggc catgcagaac ctaaatgacc gtctagcgag ctacctagaa
 300
 15 aaggtgcgga ccctggagca gtccaactcc aaacttgaag tgcaaatcaa gcagtggtag
 360
 gaaaccaacg ccccgagggc tggtcgagac tacagtgcac attacagaca aattgaagag
 420
 20 ctgcgaagtc agattaagga tgctcaactg caaatgctc ggtgtgtcct gcaaattgat
 480
 aatgctaaac tggctgctga ggacttcaga ctgaagtatg agactgagag aggaatacgt
 540
 25 ctaacagtgg aagctgatct ccaaggcctg aataaggctt ttgatgacct aaccctacat
 600
 30 aaaacagatt tggagattca aattgaagaa ctgaataaag acctagctct cctcaaaaag
 660
 gagcatcagg aggaagtcga tggcctacac aagcatctgg gcaacactgt caatgtggag
 720
 35 gttgatgctg ctccaggcct gaaccttggc gtcacatga atgaaatgag gcagaagtat
 780
 gaagtcattg cccagaagaa ccttcaagag gccaaagaac agtttgagag acagactgca
 840
 40 gttctgcagc aacaggtcac agtgaatact gaagaattaa aaggaaactga ggttcaacta
 900
 acggagctga gacgcacctc ccagagcctt gagatagaac tccagtccca tctcagcatg
 960
 45 aaagagtctt tggagcacac tctagaggag accaaggccc gttacagcag ccagttagcc
 1020
 50 aacctccagt cgctgttgag ctctctggag gcccaactga tgcagattcg gagtaacatg
 1080
 gaacgccaga acaacgaata ccatacctt cttgacataa agactcgact tgaacaggaa
 1140
 55 attgctactt accgccgctt tctggaagga gaagacgtaa aaactacaga atatcagtta
 1200

agcaccctgg aagagagaga tataaagaaa accaggaaga ttaagacagt cgtgcaagaa
 1260

5 gtagtggatg gcaaggctgt gtcattctgaa gtcaaagagg tggaagaaaa tatctaaata
 1320

~~getaaccagaa ggagatgctg ctgagggtttt gaaagaaatt tggctataat cttatctttg~~
 1380

10 ctccctgcaa gaaatcagcc ataagaaagc actattaata ctctgcagtg attagaaggg
 1440

gtgggggtggc gggaatccta tttatcagac tctgtaattg aatataaatg ttttactcag
 1500

15 aggagctgca aattgcctgc aaaaatgaaa tccagtgagc actagaatat ttaaaacatc
 1560

20 attactgcc a tctttatcat gaagcacatc aattacaagc tgtagaccac ctaatatcaa
 1620

tttgtaggta atgttcctga aaattgcaat acatttcaat tataactaaac ctcacaaagt
 1680

25 agaggaatcc atgtaaattg caaataaacc actttctaatt ttt
 1723

30 <210> 53
 <211> 4139
 <212> DNA
 35 <213> Homo sapiens

40 <400> 53
 ccgctccacc tctcaagcag ccagcgctg cctgaatctg ttctgcccc tccccacca 60
 tttcaccacc accatgacac cgggcaccca gtctccttc ttctgctgc tgctcctcac
 45 120
 agtgcttaca gttgttacag gttctgttca tgcaagctct accccaggtg gagaaaagga
 180

50 gacttcggct acccagagaa gttcagtgcc cagctctact gagaagaatg ctgtgagtat
 240
 gaccagcagc gtactctcca gccacagccc cggttcaggc tcctccacca ctcagggaca
 300

55

ggatgtcact ctggccccgg ccacggaacc agcttcaggt tcagctgcc a cctggggaca
 360
 5 ggatgtcacc tcggccccag tcaccaggcc agccctgggc tccaccaccc cgcagccca
 420
 cgatgtcacc tcagccccgg acaacaagcc agccccgggc tccaccgccc cccagccca
 480
 10 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 540
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 600
 15 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 660
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 720
 20 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 780
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 840
 25 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 900
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 960
 30 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1020
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1080
 40 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1140
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1200
 45 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1260
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1320
 50 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1380
 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 1440
 55

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1500

5 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1560

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1620

10 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1680

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1740

15 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1800

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1860

20 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1920

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 1980

25 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2040

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2100

30 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2160

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2220

40 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2280

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2340

45 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2400

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2460

50 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2520

cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca
 2580

cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 2640
 5 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 2700
 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 2760
 10 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 2820
 cggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca
 2880
 15 tggtgtcacc tcggccccgg acaacaggcc cgccttgggc tccaccgccc ctccagtcca
 2940
 caatgtcacc tcggcctcag gctctgcac aggctcagct tctactctgg tgcacaacgg
 3000
 20 cacctctgcc agggctacca caaccccagc cagcaagagc actccattct caattcccag
 3060
 ccaccactct gatactccta ccacccttgc cagccatagc accaagactg atgccagtag
 3120
 cactcaccat agctcggtag ctctctcac ctctccaat cacagcatt ctccccagtt
 3180
 30 gtctactggg gtctctttct tttcctgtc tttcacatt tcaaacctcc agtttaatto
 3240
 ctctctggaa gatcccagca ccgactacta ccaagagctg cagagagaca tttctgaaat
 3300
 35 gtttttgcag atttataaac aaggggggtt tctgggcctc tccaatatta agttcaggcc
 3360
 aggatctgtg gtggtacaat tgactctggc cttccgagaa ggtaccatca atgtccacga
 3420
 cgtggagaca cagttcaatc agtataaaac ggaagcagcc tctcgatata acctgacgat
 3480
 45 ctacagcgtc agcgtgagtg atgtgccatt tcctttctct gccagtcctg gggctggggg
 3540
 gccaggctgg ggcacgcgc tgctggtgct ggtctgtgtt ctggttgccg tggccattgt
 3600
 50 ctatctcatt gccttggctg tctgtcagtg ccgccgaaag aactacgggc agctggacat
 3660
 ctttccagcc cgggatacct accatcctat gagcgagtac cccacctacc acacccatgg
 3720
 55

EP 1 439 393 A2

gcgctatgtg cccctagca gtaccgatcg tagccctat gagaaggttt ctgcaggtaa
3780

5 cggtggcagc agcctctctt acacaaaccc agcagtggca gccgcttctg ccaacttgta
3840

gggcacgctg ccgctgagct gagtggccag ccagtgccat tccactccac tcaggttctt
3900

10 caggccagag cccctgcacc ctgtttgggc tggtagctg ggagttcagg tgggctgctc
3960

acagcctcct tcagaggccc caccaatttc tcggacactt ctcagtgtgt ggaagctcat
4020

15 gtggggccct gaggtcatg cctgggaagt gttgtggggg ctcccaggag gactggccca
4080

gagagccctg agatagcggg gatcctgaac tggactgaat aaaacgtggt ctcccactg
4139

20

<210> 54

25 <211> 15720

<212> DNA

30 <213> Homo sapiens

<400> 54

35 caaccacac cggccctgcc agccaccatg gggctgccac tagccgcct ggcggctgtg 60

tgcttgccc tgtctttggc agggggctcg gagctccaga cagagggcag aaccggatac
120

40 cacggccgca acgtctgcag cacctggggc aacttcact acaagacctt cgacggggac
180

gtcttcgct tccccggcct ctgcgactac aacttcgct ccgactgccg aggtctctac
240

45 aaggaatttg ctgtgcacct gaagcggggt ccgggccagg ctgaggcccc cgccggggtg
300

gagtccatcc tgctgacct caaggatgac accatctacc tcaccggcca cctggctgtg
360

50 cttaacgggg ccgtggtcag caccgcgcac tacagccccg ggctgctcat tgagaagagc
420

55

gatgcctaca ccaaagtcta ctcccgcgcc ggccctcacc tcattgtggaa ccgggaggat
 480
 5 gactcatgct tggagctgga cactaagttc cggaaccaca cctgtggcct ctgcggggac
 540
 tacaacggcc tgcagagcta ttcagaattc ctctctgacg gcgtgctctt cagtcccctg
 600
 10 gagtttggga acatgcagaa gatcaaccag cccgatgtgg tgtgtgagga tcccagaggag
 660
 gaggtggccc ccgcatcctg ctccgagcac cgcgccgagt gtgagaggct gctgaccgcc
 720
 15 gaggccttcg cggactgtca ggacctggtg ccgctggagc cgtatctgcg cgcctgccag
 780
 caggaccgct gccggtgccc gggcgggtgac acctgcgtct gcagcaccgt ggccgagttc
 840
 20 tcccgccagt gctccacgc cggcggccgg cccgggaact ggaggaccgc cagcgtctgc
 900
 25 cccaagacct gccccggaa cctggtgtac ctggagagcg gctcgccctg catggacacc
 960
 tgctcacacc tggaggtgag cagcctgtgc gaggagcacc gcatggacgg ctgtttctgc
 1020
 30 ccagaaggca ccgtatatga cgacatcggg gacagtggct gcgttcctgt gagccagtgc
 1080
 cactgcaggc tgcacggaca cctgtacaca ccgggccagg agatcaccaa tgactgcgag
 1140
 35 cagtgtgtct gtaacgctgg ccgctgggtg tgcaaagacc tgccctgccc cggcacctgt
 1200
 gccctggaag gcggctccca catcaccacc ttccatggga agacgtacac ctccacggg
 1260
 40 gactgctact atgtcctggc caaggggtgac cacaacgatt cctacgctct cctgggagag
 1320
 45 ctggccccct gtggctccac agacaagcag acctgcctga agacgggtgt gctgctggct
 1380
 gacaagaaga agaatgcggt ggtcttcaag tccgatggca gtgtactgct caaccagctg
 1440
 50 cagggtgaacc tgccccacgt gaccgcgagc ttctctgtct tccgccgctc ttccctaccac
 1500
 atcatggtga gcatggccat tggcgtccgg ctgcaggtgc agctggcccc agtcatgcaa
 1560

ctctttgtga cactggacca ggcctcccag gggcaggtgc agggcctctg cgggaacttc
 1620

5 aacggcctgg aaggtgacga cttcaagacg gccagcgggc tggtaggagc cacggggggc
 1680

ggctttgcca acacctggaa ggcacagtca acctgccatg acaagctgga ctggttggac
 1740

10 gatccctgct ccctgaacat cgagagcgcc aactacgccg agcactggtg ctccctcctg
 1800

aagaagacag agaccccctt tggcaggtgc cactcggctg tggaccctgc tgagtattac
 1860

15 aagaggtgca aatatgacac gtgtaactgt cagaacaatg aggactgcct gtgcgccgcc
 1920

20 ctgtcctcct acgcgcgcgc ctgcaccgcc aagggcgctc tgctgtgggg ctggcgggag
 1980

catgtctgca acaaggatgt gggctcctgc cccaactcgc aggtcttcct gtacaacctg
 2040

25 accacctgcc agcagacctg ccgctccctc tccgagggcg acagccactg tctcgagggc
 2100

tttgcgcctg tggacggctg cggtgcctt gaccacacct tcctggacga gaagggccgc
 2160

30 tgcgtacccc tggccaagtg ctctgtttac caccgcggtc tctacctgga ggcgggggat
 2220

gtggctgtca ggcaggaaga acgatgtgtg tgccgggatg ggcggctgca ctgtaggcag
 2280

35 atccggctga tcggccagag ctgcacggcc ccaaagatcc acatggactg cagcaacctg
 2340

40 actgcactgg ccacctcgaa gcccgcagcc ctcagctgcc agacgctggc cgccggctat
 2400

taccacacag agtgtgtcag tggctgtgtg tgccccgacg ggctgatgga tgacggccgg
 2460

45 ggtggctgcg tggtaggagaa ggaatgccct tgcgtccata acaacgacct gtattcttcc
 2520

ggcgccaaga tcaaggtgga ctgcaatacc tgcacctgca agagaggacg ctgggtgtgc
 50 2580

acccaggctg tgtgccatgg cacctgctcc atttacggga gtggccacta catcaccttt
 2640

55 gatgggaagt actacgactt tgacggacac tgctcctacg tggctgttca ggactactgc
 2700

ggccagaact cctcactggg ctcatcagc atcatcaccg agaacgtccc ctgtggcact
 2760

5 acgggcgta cctgctcaa ggccatcaag atcttcatgg ggaggacgga gctgaagttg
 2820

gaagacaagc accgtgtggt gatccagcgt gatgagggtc accacgtggc ctacaccacg
 2880

10 cgggaggtgg gccagtacct ggtggtggag tccagcacgg gcatcatcgt catctgggac
 2940

aagaggacca ccgtgttcat caagctggct ccctcctaca agggcacctg gtgtggcctg
 3000

15 tgtgggaact ttgaccaccg ctccaacaac gacttcacca cgcgggacca catggtggtg
 3060

agcagcgagc tggacttcgg gaacagctgg aaggaggccc ccacctgccc agatgtgagc
 3120

accaaccctg agccctgcag cctgaaccctg caccgcccgt cctggggcga gaagcagtgc
 3180

25 agcatcctca aaagcagcgt gtccagcatc tgccacagca aggtggaccc caagcccttc
 3240

tacgaggcct gtgtgcacga ctcgtgctcc tgtgacacgg gtggggactg tgagtgttc
 3300

30 tgctctgccg tggcctccta cgcccaggag tgtaccaaag agggggcctg cgtgttctgg
 3360

aggacgccgg acctgtgccc catattctgc gactactaca accctccgca tgagtgtgag
 3420

35 tggcactatg agccatgtgg gaaccggagc ttcgagacct gcaggacat caacggcatc
 3480

cactccaaca tctccgtgtc ctacctggag ggctgctacc cccggtgccc caaggacagg
 3540

cccatctatg aggaggatct gaagaagtgt gtcactgcag acaagtgtgg ctgctatgtc
 3600

45 gaggacacc actaccacc tggagcatcg gttcccaccg aggagacctg caagtctctg
 3660

gtgtgtacca actcctccca agtcgtctgc aggcggagg aaggaaagat tcttaaccag
 3720

50 acccaggatg gcgccttctg ctactgggag atctgtggcc ccaacgggac ggtggagaag
 3780

cacttcaaca tctgttccat tacgacacgc ccgtccaccc tgaccacctt caccaccatc
 3840

accctcccca ccacccccac ctcccttcacc actaccacca ccaccaccac cccgacctcc
 3900

5 agcacagttt tatcaacaac tccgaagctg tgcctgctct ggtctgactg gatcaatgag
 3960

gaccacccca gcagtggcag cgacgacggt gaccgagaac catttgatgg ggtctgcggg
 4020

10 gcccctgagg acatcgagtg caggctcggtc aaggatcccc acctcagctt ggagcagcat
 4080

15 ggccagaagg tgcagtgtga tgtctctggt gggttcattt gcaagaatga agaccagttt
 4140

ggaaatggac catttggact gtgttacgac tacaagatac gtgtcaattg ttgctggccc
 4200

20 atggataagt gtatcaccac tcccagccct ccaactacca ctcccagccc tccaccaacc
 4260

acgacgacca cccttcacc aaccaccacc cccagccctc caaccaccac cacaaccacc
 4320

25 cctccaccaa ccaccacccc cagccctcca ataaccacca cgaccacccc tctaccaacc
 4380

accactccca gccctccaat aagcaccaca accaccctc caccaaccac cactcccagc
 4440

30 cctccaacca ccactcccag ccctccaacc accactccca gccctccaac aaccaccaca
 4500

35 accaccctc caccaaccac cactcccagc cctccaatga ctacgcccat cactccacca
 4560

gccagacta ccacccttc accaaccacc actcccagcc ctccaacaac caccacaacc
 4620

40 accctccac caaccaccac tcccagtcct ccaacgacta cgcccatcac tccaccaacc
 4680

agcactacta cccttcacc aaccaccact cccagccctc caccaaccac cacaaccacc
 4740

45 cctccaccaa ccaccactcc cagccctcca acaaccacca ctcccagtc tccaacaatc
 4800

accacaacca cccttcacc aaccaccact cccagccctc caacaacgac cacaaccacc
 4860

50 cctccaccaa ccaccactcc cagccctcca acgactacac ccactactcc accaaccagc
 4920

55 actaccacc ttccaccaac caccactccc agccctccac caaccaccac aaccaccct
 4980

ccaccaacca ccaactcccag ccctccaaca accaccactc ccagccctcc aataaccacc
 5040

5 acaaccaccc ctccaccaac caccactccc agctctccaa taaccaccac tcccagccct
 5100

ccaacaacca ccatgaccac cccttcacca accaccaccc ccagctctcc aataaccacc
 5160

10 acaaccaccc ctctctcaac taccactccc agccctccac caaccaccat gaccaccct
 5220

tcaccaacca ccaactcccag ccctccaaca accaccatga ccacccctcc accaaccacc
 15 5280

acttcagcc ctctaacaac tactctcta cctccatcaa taactctcc tacattttca
 5340

20 ccattctcaa cgacaacccc tactacccca tgcgtgcctc tctgcaattg gactggctgg
 5400

ctggattctg gaaaacccaa ctttcacaaa ccagggtggag acacagaatt gattggagac
 5460

25 gtctgtggac caggctgggc agctaacatc tcttgagag ccaccatgta tcctgatgtt
 5520

cccattggac agcttggaca aacagtgggtg tgtgatgtct ctgtggggct gatatgcaaa
 30 5580

aatgaagacc aaaagccagg tggggtcatc cctatggcct tctgcctcaa ctacgagatc
 5640

35 aacgttcagt gctgtgagtg tgtcacccaa cccaccacca tgacaaccac caccacagag
 5700

aacccaactc cgccaaccac gacacccatc accaccacca ctacggtgac cccaacccca
 5760

40 acaccaccg gcacacagac cccaaccacg acaccatca ccaccaccac tacggtgacc
 5820

ccaaccccaa caccacccg cacacagacc ccaaccacga caccatcac caccaccact
 45 5880

acggtgaccc caaccccaac acccaccggc acacagaccc caaccacgac acccatcacc
 5940

50 accaccacta cggtgacccc aaccccaaca cccaccggca cacagacccc aaccacgaca
 6000

cccatcacca ccaccactac ggtgaccca accccaacac ccaccggcac acagacccca
 6060

55 accacgacac ccatcaccac caccactacg gtgaccccaa cccaacacc caccggcaca
 6120

cagaccccaa ccacgacacc catcaccacc accactacgg tgaccccaac cccaacaccc
6180

5 accggcacac agaccccaac cagcagacccc atcaccacca ccactacggt gaccccaacc
6240

ccaacaccca ccggcacaca gaccccaacc acgacaccca tcaccaccac cactacggtg
6300

10 accccaaccc caacacccac cggcacacag accccaacca cgacacccat caccaccacc
6360

actacggtga cccaaccccc aacaccacc ggcacacaga cccaaccac gacacccatc
15 6420

accaccacca ctacggtgac cccaacccca acaccaccg gcacacagac cccaaccacg
6480

20 acacccatca ccaccaccac tacggtgacc ccaaccccaa caccaccgg cacacagacc
6540

ccaaccacga caccatcac caccaccact acggtgaccc caaccccaac acccaccggc
6600

25 acacagaccc caaccagac acccatcacc accaccacta cggtgacccc aaccccaaca
6660

cccaccggca cacagacccc aaccacgaca cccatcacca ccaccactac ggtgacccca
30 6720

accccaacac ccaccggcac acagacccca accacgacac ccatcaccac caccactacg
6780

35 gtgaccccaa cccaacacc caccggcaca cagaccccaa ccacgacacc catcaccacc
6840

accactacgg tgaccccaac cccaacaccc accggcacac agaccccaac cagcagaccc
6900

40 atcaccacca ccactacggt gaccccaacc ccaacaccca ccggcacaca gaccccaacc
6960

acgacaccca tcaccaccac cactacggtg accccaaccc caacacccac cggcacacag
7020

45 accccaacca cgacacccat caccaccacc actacggtga cccaaccccc aacaccacc
7080

ggcacacaga cccaaccac gacacccatc accaccacca ctacggtgac cccaacccca
50 7140

acaccaccg gcacacagac cccaaccacg acacccatca ccaccaccac tacggtgacc
7200

55 ccaaccccaa caccaccgg cacacagacc ccaaccacga ccccatcac caccaccact
7260

acggtgaccc caacccaac acccaccggc acacagaccc caaccacgac acccatcacc
 7320

5 accaccacta cggtgacccc aacccaaca cccaccggca cacagacccc aaccacgaca
 7380

cccatcacca ccaccactac ggtgacccca accccaacac ccaccggcac acagacccca
 7440

10 accacgacac ccatcaccac caccactacg gtgaccccaa cccaacacc caccggcaca
 7500

cagaccccaa ccacgacacc catcaccacc accactacgg tgaccccaac cccaacacc
 15 7560

accggcacac agacccaac cacgacaccc atcaccacca cactacgggt gacccaacc
 7620

20 ccaacaccca ccggcacaca gacccaacc acgacaccca tcaccaccac cactacgggtg
 7680

accccaaccc caacacccac cggcacacag accccaacca cgacacccat caccaccacc
 7740

25 actacgggtga cccaacccc aacaccacc ggcacacaga cccaaccac gacacccatc
 7800

accaccacca ctacgggtgac cccaacccca acaccaccg gcacacagac cccaaccacg
 30 7860

acacccatca ccaccaccac tacggtgacc ccaaccccaa caccaccggg cacacagacc
 7920

35 ccaaccacga caccatcac caccaccact acggtgaccc caacccaac acccaccggc
 7980

acacagaccc caaccacgac acccatcacc accaccacta cggtgacccc aacccaaca
 8040

40 cccaccggca cacagacccc aaccacgaca cccatcacca ccaccactac ggtgacccca
 8100

accccaacac ccaccggcac acagacccca accacgacac ccatcaccac caccactacg
 8160

45 gtgaccccaa cccaacacc caccggcaca cagaccccaa ccacgacacc catcaccacc
 8220

accactacgg tgaccccaac cccaacacc accggcacac agacccaac cacgacacc
 50 8280

atcaccacca cactacgggt gacccaacc ccaacaccca ccggcacaca gacccaacc
 8340

55 acgacaccca tcaccaccac cactacgggtg accccaaccc caacacccac cggcacacag
 8400

accccaacca cgacacccat caccaccacc actacggtga cccaacccc aacaccacc
 8460

5 ggcacacaga cccaaccac gacacccatc accaccacca ctacggtgac cccaaccca
 8520

acaccaccg gcacacagac cccaaccag acaccatca ccaccaccac tacggtgacc
 8580

10 ccaacccaa caccaccgg cacacagacc ccaaccacga caccatcac caccaccact
 8640

acggtgaccc caacccaac accaccggc acacagaccc caaccagac acccatcacc
 8700

15 accaccacta cggtgacccc aacccaaca cccaccggca cacagacccc aaccagaca
 8760

cccatcacca ccaccactac ggtgaccca acccaacac ccaccggcac acagaccca
 8820

accacgacac ccatcaccac caccactacg gtgacccaa cccaacacc caccggcaca
 8880

25 cagacccaa ccacgacacc catcaccacc accactacgg tgaccccaac cccaacacc
 8940

accggcacac agacccaac cagcacccc atcaccacca cactacggt gacccaacc
 9000

30 ccaacaccca cgggcacaca gacccaacc acgacacca tcaccaccac cactacggtg
 9060

accccaacc caacaccac cggcacacag acccaacca cgacacccat caccaccacc
 9120

actacggtga cccaacccc aacaccacc ggcacacaga cccaaccac gacacccatc
 9180

40 accaccacca ctacggtgac cccaaccca acaccaccg gcacacagac ccaaccacg
 9240

acaccatca ccaccaccac tacggtgacc ccaacccaa caccaccgg cacacagacc
 9300

45 ccaaccacga caccatcac caccaccact acggtgaccc caacccaac acccaccggc
 9360

acacagaccc caaccagac acccatcacc accaccacta cggtgacccc aacccaaca
 9420

50 cccaccggca cacagacccc aaccagaca cccatcacca ccaccactac ggtgaccca
 9480

accccaacac ccaccggcac acagaccca accacgacac ccatcaccac caccactacg
 9540

gtgaccccaa ccccaacacc caccggcaca cagaccccaa ccacgacacc catcaccacc
9600

5 accactacgg tgaccccaac cccaacaccc accggcacac agaccccaac caccgacacc
9660

atcaccacca ccactacggt gacccaacc ccaacaccca ccggcacaca gacccaacc
9720

10 acgacaccca tcaccaccac cactacggtg acccaaccc caacacccac cggcacacag
9780

acccaacca cgacacccat caccaccacc actacggtga cccaacccc aacaccacc
9840

15 ggcacacaga cccaaccac gacacccatc accaccacca ctacggtgac cccaaccca
9900

20 acaccaccg gcacacagac ccaaccacg acaccatca ccaccaccac tacggtgacc
9960

ccaaccccaa caccaccgg cacacagacc ccaaccacga caccatcac caccaccact
10020

25 acggtgacc caaccccaac accaccggc acacagacc caaccagac acccatcacc
10080

accaccacta cggtgacccc aacccaaca cccaccggca cacagacccc aaccagaca
10140

30 cccatcacca ccaccactac ggtgaccca acccaaacac ccaccggcac acagaccca
10200

accagacac ccacaccac caccactacg gtgacccaa cccaacacc caccggcaca
10260

35 cagaccccaa ccacgacacc catcaccacc accactacgg tgaccccaac cccaacacc
10320

40 accggcacac agaccccaac caccgacacc atcaccacca ccactacggt gacccaacc
10380

ccaacaccca ccggcacaca gacccaacc acgacaccca tcaccaccac cactacggtg
10440

45 acccaaccc caacaccac cggcacacag acccaacca cgacacccat caccaccacc
10500

actacggtga cccaacccc aacaccacc ggcacacaga cccaaccac gacacccatc
10560

50 accaccacca ctacggtgac ccaaccca acaccaccg gcacacagac ccaaccacg
10620

55 acaccatca ccaccaccac tacggtgacc ccaacccaa caccaccgg cacacagacc
10680

ccaaccacga caccatcac caccaccact acggtgaccc caacccaac acccaccggc
10740

5 acacagaccc caaccacgac acccatcacc accaccacta cggtgacccc aacccaaca
10800

cccaccggca cacagacccc aaccacgaca cccatcacca ccaccactac ggtgaccca
10860

10 accccaacac ccaccggcac acagaccca accacgacac ccatcaccac caccactacg
10920

gtgaccccaa cccaacacc caccggcaca cagacccaa ccacgacacc catcaccacc
15 10980

accactacgg tgacccaac cccaacacc accggcacac agacccaac cagacaccc
11040

20 atcaccacca ccactacggt gacccaacc ccaacacca ccggcacaca gacccaacc
11100

acgacacca tcaccaccac cactacggtg acccaaccc caacaccac ccggcacag
11160

25 accccaacca cgacaccat caccaccacc actacggtga cccaacccc aacaccacc
11220

ggcacacaga cccaaccac gaccccatc accaccacca ctacggtgac cccaaccca
30 11280

acaccaccg gcacacagac cccaaccag acaccatca ccaccaccac tacggtgacc
11340

35 ccaacccaa caccaccgg cacacagacc ccaaccacga ccccatcac caccaccact
11400

acggtgaccc caacccaac acccaccggc acacagaccc caaccacgac acccatcacc
11460

40 accaccacta cggtgacccc aacccaaca cccaccggca cacagacccc aaccacgaca
11520

ccatcacca ccaccactac ggtgaccca accccaacac ccaccggcac acagaccca
45 11580

accacgacac ccatcaccac caccactacg gtgacccaa cccaacacc caccggcaca
11640

cagacccaa ccacgacacc catcaccacc accactacgg tgacccaac cccaacccc
50 11700

accggcacac agacccaac cagacaccc atcaccacca ccactacggt gacccaacc
11760

55 ccaacacca ccggcacaca gacccaacc acgacacca tcaccaccac cactacggtg
11820

accccaaccc caacacccac cggcacacag accccaacca cgacacccat caccaccacc
 11880

5 actacggtga cccaacccc aacaccacc ggcacacaga cccaaccac gacaccatc
 11940

accaccacca ctacggtgac cccaaccca acaccaccg gcacacagac cccaaccag
 12000

10 acaccatca ccaccaccac tacggtgacc ccaacccaa caccaccgg cacacagacc
 12060

ccaaccacga caccatcac caccaccact acggtgaccc caacccaac acccaccggc
 12120

15 acacagacc caaccagac acccatcacc accaccacta cggtgacccc aacccaaca
 12180

cccaccggca cacagacccc aaccacgaca cccatcacca ccaccactac ggtgaccca
 12240

accccaacac ccaccggcac acagaccca accacgacac ccatcaccac caccactacg
 12300

25 gtgacccaa cccaacacc caccggcaca cagacccaa ccacgacacc catcaccacc
 12360

accactacgg tgacccaac ccaacaccc accggcacac agacccaac cagcacacc
 12420

30 atcaccacca ccactacggt gacccaacc ccaacaccca cggcacaca gacccaacc
 12480

acgacaccca tcaccaccac cactacggtg acccaaccc caacaccac cggcacacag
 12540

accccaacca cgacacccat caccaccacc actacggtga cccaacccc aacaccacc
 12600

40 ggcacacaga cggggcccc caccacaca agcacagcac cgattgctga gttgaccaca
 12660

tccaatctc cgctgagtc ctcaaccct cagacctctc ggtccacctc tccccctc
 12720

45 acggagtcaa ccacccttct gagtacccta ccactgcca ttgagatgac cagcacggc
 12780

ccaccctca caccacggc acccagacc acgagcggag gccacacact gtctccaccg
 12840

cccagacca ccacgtcccc tccaggcacc cccactcgcg gtaccacgac cgggtcatct
 12900

55 tcagcccca cccacgac tgtgcagacg accaccacca gtgcctggac ccaacgccg
 12960

accccactct ccacacccag catcatcagg accacaggcc tgaggcccta cccttcctct
 13020
 5 gtgcttatct gctgtgtcct gaacgacacc tactacgcac caggtgagga ggtgtacaac
 13080
 ggcacatacg gagacacctg ttatttcgtc aactgctcac tgagctgtac gttggagtcc
 13140
 10 tataactggc cctgcccata cacgccctcc ccaacaccca cgccctccaa gtcgacgccc
 13200
 acgccttcca agccatcgtc cacgccctcc aagccgacgc ccggcaccaa gcccccgag
 13260
 15 tgcccagact ttgatcctcc cagacaggag aacgagactt ggtggctgtg cgactgcttc
 13320
 atggccacgt gcaagtacaa caacacggtg gagatcgtga aggtggagtg tgagccgccg
 13380
 cccatgccca cctgctccaa cggcctccaa cccgtgcgcg tcgaggaccc cgacggctgc
 13440
 25 tgctggcact gggagtgcga ctgctactgc acgggctggg gcgacccgca ctatgtcacc
 13500
 ttcgacggac tctactacag ctaccagggc aactgcacct acgtgctggt ggaggagatc
 13560
 30 agccctccg tggacaactt cggagtctac atcgacaact accactgcga tcccaacgac
 13620
 aaggtgtcct gtccccgcac cctcatcgtg cgccacgaga cccaggaggt gctgatcaag
 13680
 accgtgcata tgatgccat gcaggtgcag gtgcaggtga acaggcaggc ggtggcactg
 13740
 40 ccctacaaga agtacgggtt ggaggtgtac cagtctggca tcaactacgt ggtggacatc
 13800
 cccgagctgg gtgtcctcgt ctctacaat ggctgtcct tctccgtcag gctgccctac
 13860
 45 caccggtttg gcaacaacac caagggccag tgtggcacct gcaccaacac cacctccgac
 13920
 gactgcattc tgcccagcgg ggagatcgtc tccaactgtg aggctgcggc tgaccagtgg
 13980
 50 ctggtgaacg acccctccaa gccacactgc cccacagca gctccacgac caagcgcccg
 14040
 gccgtcactg tgcccggggg cggtaaaacg accccacaca aggactgcac cccatctccc
 14100

ctctgccagc tcatcaagga cagcctgttt gcccagtgcc acgcactggg gccccgcag
 14160
 5 cactactacg atgcctgcgt gttcgacagc tgcttcatgc cgggctcgag cctggagtgc
 14220
 gccagtctgc aggcctacgc agccctctgt gcccagcaga acatctgcct cgactggcgg
 14280
 10 aaccacacgc atggggcctg cttggtggag tgcccatctc acagggagta ccaggcctgt
 14340
 ggccctgcag aagagccac gtgcaaacc agtcctccc agcagaaca cacagtccg
 14400
 15 gtggaaggct gcttctgtcc tgagggcacc atgaactacg ctcttggtt tgatgtctgc
 14460
 gtgaagacct gcggctgtgt gggacctgac aatgtgcca gagagtttg ggagcacttc
 20 14520
 gagttcgact gcaagaactg tgtctgcctg gagggtgaa gtggcatcat ctgccaaccc
 14580
 25 aagaggtgca gccagaagcc cgttaccac tgctggaag acggcaccta cctcgccacg
 14640
 gaggtcaacc ctgccgacac ctgctgcaac attacgtct gcaagtgaa caccagcctg
 14700
 30 tgcaaagaga agccctcgt gtgcccgtg ggattcgaag tgaagagcaa gatggtgcct
 14760
 ggaaggtgct gtcccttcta ctggtgtgag tccaagggg tgtgtgttca cggaatgct
 35 14820
 gagtaccagc ccggttctcc agttattcc tccaagtgc aggactgcgt gtgcacggac
 14880
 40 aaggtggaca acaacacct gctcaacgtc atgcctgca cccacgtgc ctgcaacacc
 14940
 tcctgcagcc ctggcttoga actcatggag gccccgggg agtgctgtaa gaagtgtgaa
 15000
 45 cagacgcact gtatcatcaa acggcccgac aaccagcac tcatcctgaa gcccggggac
 15060
 ttcaagagcg acccgaagaa caactgcaca ttcttcagct gcgtgaagat ccacaaccag
 50 15120
 ctcatctcgt ccgtctcaa catcacctgc cccaactttg atgccagcat ttgcatccc
 15180
 55 ggctccatca cattcatgcc caatgatgc tgcaagacct gcaccctcg caatgagacc
 15240

EP 1 439 393 A2

aggggtgccct gctccaccgt ccccgtcacc acggagggtt cgtacgccgg ctgcaccaag
15300

5 accgtcctca tgaatcattg ctccgggtcc tgcgggacat ttgtcatgta ctcgccaag
15360

gcccaggccc tggaccacag ctgctcctgc tgcaaagagg agaaaaccag ccagcgtgag
15420

10 gtggtcctga gctgccccaa tggcggctcg ctgacacaca cctacacca catcgagagc
15480

tgccagtgcc aggacaccgt ctgcgggctc cccaccggca cctccgccg ggcccggcgc
15540

15 tcccctaggc atctggggag cgggtgagcg gggtgggcac agccccctc actgccctcg
15600

20 acagctttac ctccccgga ccctctgagc ctctaagct cggttcctc tcttcagata
15660

tttattgtct gagtctttgt tcagtccttg ctttccaata ataaactcag ggggacatgc
15720

25

30

<210> 55

35 <211> 4707

<212> DNA

<213> Homo sapiens

40

<400> 55

45 gatcaccatc accgagacca cctcacacag tactcccagc tacactacct caatcaccac 60

caccgagacc ccctcacaca gtactcccag ctacactacc tcaatcacca ccaccgagac
120

50 cccatcacac agtactccca gcttcacttc ttcaatcacc accaccgaga ccacatccca
180

cagtactccc agcttcactt cttcaatcag gaccaccgag accacatcct acagtactcc
240

55

cagcttcact ttttcaaata ccatcactga gaccacctca cacagtactc ccagctacat
 300
 5 tacctcaatc accaccaccg agacccctc aagcagtact cccagcttca gttcttcgat
 360
 caccaccact gagaccacat cccacagtac tcccggcttc actttttcaa tcaccaccac
 420
 10 tgagactaca tcccacagta ctcccagctt cactttctcg atcaccacca ctgagaccac
 480
 ctcacatgat actcccagct tcactttctc aatcaccacc agtgagaccc cctcacacag
 540
 15 tactcccagc tccacttctt taatcaccac caccaagacc acctcacaca gtactcccag
 600
 cttcacttct tcgatcacca ccaccgagac cacctcacac agtgctcgca gcttcacttc
 660
 20 ttgatcacc accaccgaga ccacctcaca caatactcgg agcttcactt cttgatcac
 720
 25 caccaccgag accaactctc acagtactac cagcttcact tcttcgatca ccaccaccga
 780
 gaccacctca cacagtactc ccagcttcag ttcttcaatc accaccactg agacccctt
 840
 30 acacagtact cctggcctac cttcgtgggt caccaccacc aagaccacct cacacattac
 900
 35 tcctggcctc actttctcaa tcaccaccac tgagactacc tcacacagta ctcccggctt
 960
 cactttctca atcaccacca ctgagaccac ctgagagagt actcccagcc tcagttcttc
 1020
 40 aaccatctac tccacagtca gcacatccac aactgccatc acctcacatt ttactacctc
 1080
 agagactgcg gtgactccca cacctgtaac cccatcttct ctgagtacag acatcccga
 1140
 45 cacaagccta cgaactctca ccccttcgtc tgtgggcacc agcacttcac tgactacaac
 1200
 cacagacttt cctctatac ccaactgatc cagtacctta ccaactcgaa cacacatcat
 1260
 50 ttcatcttct cctccatcc aaagtacaga aacctcatcc cttgtgggca ccacctctcc
 1320
 55 caccatgtcc actgtgagaa tgacctcag aattactgag aacaccccaa tcagttcctt
 1380

tagcacaagt attgttggtta tacctgaaac cccaacacag acccctcctg tactgacgtc
 1440

5 agccactggg acccaaacat ctccctgcacc tactactgtc acctttggaa gtacggattc
 1500

ctccacgtcc actcttcata ctcttactcc atcaacagcc ttgagcacga tcgtgtcaac
 1560

10 atcacagggt cctattccta gcacacattc ctccaccctt caaacaactc cttctactcc
 1620

ctcattgcaa acttcactca catctacaag tgagttcact acagaatctt tcactagggg
 15 1680

aagtacgtct acaaatgcaa tcttgacttc ttttagtacc atcatctggt cctcaacacc
 1740

20 cactattatc atgtcctctt ctccatcttc tgccagcata actccagtgt tctccactac
 1800

cattcattct gttccttctt caccatacat tttcagtaca gaaaatgtgg gctccgcttc
 1860

25 tatcacaggg tttcctagtc tctcttcctc tgcaactacc agcacttctt caaccagctc
 1920

ctctctgacc acagctctca ctgaaataac ccccttttct tatatttccc ttccctccac
 30 1980

cacaccctgt ccaggaacta taacaattac catagtccct gcctctccca ctgatccatg
 2040

35 tgttgaaatg gatcccagca ctgaagctac ttctcctccc accaccccat taacagtctt
 2100

tccctttact accgaaatgg tcacctgtcc tacctccatc agtatccaaa ctactcttac
 2160

40 tacatatatg gacacttctt ccatgatgcc agaaagtgag tccagcatct cacccaatgc
 2220

ttccagttcc actggcactg ggactgtacc cacaaacaca gttttcaca gtactcgact
 2280

45 gccaccagt gagacctggc tgagcaacag ttctgtgatc cccctacctc ttctggcgt
 2340

ctctaccatc ccgctcacca tgaaaccaag cagtagcctc ccgaccatcc tgaggacttc
 50 2400

aagcaagtca acacacccat cccacccac cactaggact tcagagacac cagtggccac
 2460

55 taccagact cctaccacc ttacatcacg caggacaact cgcatactt ctcatgatgac
 2520

cacacagtcc acgttgacca ccactgcagg cacctgtgac aatggtggca cctgggaaca
 2580
 5 gggccagtgt gcttgcccttc cgggggttttc tggggaccgc tgtcagctcc agaccagatg
 2640
 ccagaatggg ggtcagtggg atggcctcaa atgccagtgc cccagcacct tctatgggtc
 2700
 10 cagttgtgag tttgctgtgg aacagggtgga tctagatgca gaagattttt gcagacatgc
 2760
 agggcttcac cttcaagggt gtggagatcc tgtccctgag gaatggcagc atcgtggtgg
 2820
 15 actacctggt cctgctggag atgcccttca gccccagct ggagagcgag tatgagcagg
 2880
 20 tgaagaccac gctgaaggag gggctgcaga acgccagcca ggatgtgaac agctgccagg
 2940
 actcccagac cctgtgtttt aagcctgact ccatcaagggt gaacaacaac agcaagacag
 3000
 25 agctgacccc ggcagccatc tgccgcgcgc cgctcccacg ggctatgaag agttctactt
 3060
 ccccttggtg gaggccaccc ggctccgctg tgtcaccaaa tgcacgtctg ggggtggaaa
 3120
 30 cgccatcgac tgtcaccagg gccagtgcgt tctggagacg agcgggtccca cgtgtcgctg
 3180
 ctactccacc gacacgcact ggttctctgg ccgcgctgc gaggtggccg tccactggag
 3240
 35 ggcgctggtc ggggcctgac ggccggcgcg cgctgctggt gctgctgctc gtggcgctgg
 3300
 40 gcgtccgggc ggtgcgctcc ggatggtggg gcggccagcg ccgaggccgg tccctgggacc
 3360
 aggacaggaa atggttcgag acctgggatg aggaagtcgt gggcactttt tcaaactggg
 3420
 45 gtttcgagga cgacggaaca gacaaggata caaatttcta tgtggccttg gagaacgtga
 3480
 caccactatg aaggtgcaca tcaagagacc cgagatgacc tcgtcctcag tgtgagcctg
 3540
 50 cggggccctt tcaccacccc ctccgccctg ccccgacac aagggtctgc attgcgtcca
 3600
 55 tttcaagagg tgaccccagg acgcgggcag cccaggctcc tgctgttctt gggcaagatg
 3660

agactgttcc cccaaatccc atccttctcc ttccaacttg gctgaaaccc acctggagac
3720

5 gcagttcacg tccaggctct tccactgtgg aatcttgggc aagtcagtaa cgagcctcag
3780

tttcctcacc tgcaaaacgg gtacagcatt cctgtatgat acgtcacgcc gttgttgtga
3840

10 aaaccacata gacttggtea attctcggtc ctactctgcc ctcccgtctc agccctcgtg
3900

ttgccattgc ctctctcgga tectccaatc ctcacgtcct tcacctggtc tctggccctg
15 3960

gttcttattt tctctcaatt ccctactgcc tgtttcttac tttgaacctg gaggcagcct
4020

20 gcagcccat cccatctcct gccctctcct gatctaactc cctgctgcat ctcttgctcc
4080

cattccttag acgtcctccc cttttgacct cgttccttca tccatcctgc acccagtc
4140

25 ccagcccta aatcctcct cctctcctca catcctggcc cctagcaagg tatagatagc
4200

ctctgtgtct taggataccc cgggtgctgt tccctcggtc atcctgttgc ccagttcccc
30 4260

gtttctcttg ctctcattcc tgtatccttt ccccttttga gcccgccat tcatcggttc
4320

35 tgccccgac tccccagcc ctaaataccc cagctgctgt tcccccatc accctgctgc
4380

ccaattcttt attctccacc cctttctctc acccctggag ccctgcgggt gggggcaggg
4440

40 catgagttcc ccagtcacca aggaaaggca gcccctcag tctccctcct cctcattccc
4500

ttccatctcc ctcccctctg ccttttaaac ccatcccctc cgattcccct cctccccct
4560

45 ctctccctgg tgtcacctgg attcctgcag taattctgag cccttgaaat cctcagtcgc
4620

cttggcgggg aagattggct ttggggacag gaggtcggca catctccagg tcttcatgtg
50 4680

cgcaatatag agtttattgt aaaaagc
4707

55

<210> 56
 <211> 4151
 5 <212> DNA
 <213> Homo sapiens
 10
 <400> 56
 gggacagggc actcttcccc gccgtccaca caatgagtgt tggccggagg aagctggccc 60
 15 tgctctgggc cctggctctc gctctggcct gcacccggca tacaggccat gccaggatg
 120
 gctcctccga atccagctac aagcaccacc ctgccctctc tccatcgcc cgggggcccc
 20 180
 tcggggtccc gctccgtggg gcgactgtct tccatctct gaggaccatc cctgtggtac
 240
 gagcctccaa cccggcgcac aacgggcggg tgtgcagcac ctggggcagc ttccactaca
 25 300
 agaccttga cggcgacgtc ttccgcttcc ccggcctctg caactacgtg ttctccgagc
 360
 30 actgcggtgc cgcctacgag gattttaaca tcccagctac gccgcagcca ggagtcagcg
 420
 gccccacgc tgagcagggt cctcatgaag gtggatggcg tggatcca gctgaccaag
 35 480
 ggctccgtcc tggtaacgg ccacccggc ctgctgccct tcagccagtc tggggtcctc
 540
 attcagcaag agcagcagct acaccaaggt ggaagccagg ctgggccttg tcctcatgtg
 40 600
 gaaccagat gacagcctgc tgctggaagc tggacaccaa atacgccaac aagaacctgt
 660
 45 gggctctgtg gggacttcaa cgggatgcc gtggtcagcg agctcctctc ccacaacacc
 720
 aagctgacac ccatggaatt cgggaacctg ccgaaagatg gacgaacca cggagcagtg
 780
 50 tcaggaccct gtccctgaac ccccgaagaa ctgctccact ggctttggca tcctgtgagg
 840
 agctcctgca cggccagctg ttctctggct gcgtggcctt ggtggacgtc ggcagctacc
 55 900

tggaggcttg caggcaagac ctctgcttct gtgaagacac cgacctgctc agctgcgtct
 960

5 gccacaccct tgccgagtag tcccggcagt gcacccatgc agggggggtg cccagagact
 1020

ggcgggggccc tgactttctgc cccagaagt gccccaacaa catgcagtag cacgagtgcc
 1080

10 gctccccctg cgcagacacc tgctccaacc aggagcactc ccgggcctgt gaggaccact
 1140

gtgtggccgg ctgcttctgc cctgagggga cgggtgctga cgacatcggc cagaccggct
 1200

15 gtgtccctgt gtcaaagtgt gcctgcgtct acaacggggc tgcctatgcc ccagggggcca
 1260

cctactccac agactgcacc aactgcacct gctccggagg ccggtggagc tgccaggaag
 1320

ttccatgccc gggtagctgc tctgtgcttg gaggtgcca cttctcaacg tttagcggga
 1380

25 agcaatacac ggtgcacggc gactgcagct atgtgctgac caagccctgt gacagcagtg
 1440

ccttcaactgt actggctgag ctgcgcaggt gcgggctgac ggacagcgag acctgcctga
 1500

30 agagcgtgac actgagcctg gatggggcgc agacgggtgt ggtgatcaag gccagtgggg
 1560

aagtgttctt gaaccagatc tacaccacgc tgccatctc tgcagccaac gtcaccatct
 1620

tcagaccctc aaccttcttc atcatcgccc agaccagcct gggcctgcag ctgaacctgc
 1680

40 agctggtgcc caccatgcag ctgttcatgc agctggcgcc caagctccgt gggcagacct
 1740

gcggtctctg tgggaacttc aacagcatcc aggccgatga cttccggacc ctcaagtggg
 1800

45 tgggtggaggc caccgctgcg gccttcttca acaccttcaa gaccagggc gcctgcccc
 1860

acatcaggaa cagcttcgag gaccctgct ctctgagcgt ggagaatgag aagtatgctc
 1920

50 agcactggtg ctgcagctg accgatgccg acggccctt cggccggtgc catgctgccg
 1980

tgaagccggg aacctactac tcgaactgca tgtttgacac ctgcaactgt gagcggagcg
 2040

aggactgcct gtgcgccg cgctcctcct acgtgcacgc ctgtgccgcc aaggcgctgc
2100

5 agctcggcgg ctggaggagc ggcgtctgca cgaagcctat gaccacttgc cccaagtcaa
2160

tgacgtacca ctaccatgtc agcacctgcc agcccacctg ccgctccctg agcgaggggg
2220

10 acatcacctg cagtgttggc ttcaccccg tggatggctg catctgtccc aagggcacct
2280

tcttggaaga cacgggcaag tgtgtgcagg ccagcaactg tccctgctac cacagaggct
15 2340

ccatgatccc caatggggag tcgggtgcacg acagcggggc tatctgcacc tgcacacatg
2400

20 ggaagctgag ctgcatcga ggccaagccc ccgcccagc gtgtgctgcg cccatggtgt
2460

tctttgactg ccgaaatgcc acgcccggg acacaggggc tggctgtcag aagagctgcc
2520

25 acacactgga catgacctgt tacagcccc aatgtgtgcc tggctgcgtg tgccccgacg
2580

ggctggtggc ggacggcgag ggcggctgca tcaactgcga ggactgcccc tgcgtgcaca
30 2640

atgaggccag ctaccgggcc ggccagacca tccgggtggg ctgcaacacc tgcacctgtg
2700

35 acagcaggat gtggcggtgc acagatgacc cctgcctggc cacctgcgcc gtgtacgggg
2760

acggccacta cctcaccttc gacggacaga gctacagctt caacgaggag actgcgagta
2820

40 ctgctggtg cagaaccgct gtggcgggaa agacagcacc caggactcct ttcgtgttgt
2880

caccgagaac gtcccctgcg gcaccacagg gaccacctgc tccaaggcca tcaagatttt
2940

45 cctgggggaa cttcgagctg aagctaagcc atgggaaggt ggaggtgatc gggacggacg
3000

agagccagga ggtgccatac accatccggc agatgggcat ctacctggtg gtggacaccg
50 3060

acattggcct ggtgctgctg tgggacaaga agaccagcat cttcatcaac ctacgccccg
3120

55 agttcaaggc cagggtctgc ggctgtgtg ggaacttcga cgacatcgcc gttaatgact
3180

ttgccacgcg gagccggtct gtggtggggg acgtgctgga gtttgggaac agctggaagc
 3240

5 tctccccctc ctgccagat gccctggcgc ccaaggaccc ctgcacggcc aacccttcc
 3300

gcaagtccctg ggcccagaag cagtgcagca tcctccacgg cccacacctc gccgcctgcc
 3360

10 acgcacacgt ggagccggcc aggtactacg aggcctgcgt gaacgacgcg tgcgcctgcg
 3420

15 actccggggg tgactgcgag tgcttctgca cggctgtggc ccgctacgcc caggcctgcc
 3480

atgaagtagg cacctgtgtg tgtctgcgga cccaagcat ctgccctctg ttctgcgact
 3540

20 actacaaccc cgaaggccag tgcgagtggc actaccagcc ctgcggggtg ccctgcctgc
 3600

gcacctgccg gaacccccgt ggagactgcc tgcgggacgt ccggggcctg gaaggctgct
 3660

25 accccaagtg cccaccagag gctcccatct ttgatgagga caagatgcag tgtgtggcca
 3720

cctgcccac cccgcctctg ccaccacggt gccacgtcca tgggaagtcc taccggccag
 3780

30 gtgcagtggg gccctcggac aagaactgcc agtctgcct ttgtaaggag cgcggcgtgg
 3840

35 agtgcaccta caaagctgag gcctgtgtct gcacctaca tggacagcgc ttccaccag
 3900

gggacgtcat ctaccacacg acggatggca cgggtggctg catctccgcc cgctgcgggg
 3960

40 ccaacggcac cattgagagg aggtctacc cctgcagccc caccaccct gtcccccaa
 4020

ccacattctc cttctccaca ccccgttg tcgtgagctc cacgcacacc ccagcaatg
 4080

45 gcccaagcag cgcgcacaca ggccctccga gcagcgctg gccaccaca gcaggcactt
 4140

50 ctcccaggac g
 4151

<210> 57

55 <211> 880

<212> DNA

<213> Homo sapiens

5

<400> 57

10 tccagcactt tgctcgggtc acggcctcct cctgggtccc aggacccac cataggcaga 60

ggcaggcctt cctacaccct actccctgtg cctccaggct cgactagtcc ctagcactcg
120

15 acgactgagt ctctgagatc acttcaccgt ggtctccgcc tcacccttgg cgctggacca
180

gtgagaggag agggctgggg cgctccgtg agccactcct gcgccccctt ggccttgtct
240

20 acctcttgcc ccccgagggt ttagtgtcga gctcacccca gcctcctaca acctcctggt
300

ggccttgccg cccccacaac cccgaggtat aaagccagggt acacgaggca ggggacgcac
360

25

caaggatgga gatgttcag gggctgctgc tgttgctgct gctgagcatg ggcgggacat
420

30 gggcatccaa ggagccgctt cggccacgggt gccgccccat caatgccacc ctggtgtggt
480

agaaggagggt ctgccccgtg tgcctaccg tcaacaccac catctgtgcc ggctactgcc
540

35

ccaccatgac ccgcgtgctg caggggggtcc tgccggccct gcctcagggtg gtgtgcaact
600

accgcgatgt gcgcttcgag tccatccggc tccctggctg cccgcgcggc gtgaaccccg
660

40

tggtctccta cgccgtgggt ctgagctgtc aatgtgcact ctgccgccgc agcaccactg
720

actgcggggg tccaaggac cacccttga cctgtgatga ccccgettc caggactcct
780

45

cttcctcaaa ggcccctccc cccagccttc caagtccatc ccgactcccg gggccctcgg
840

50

acaccccgat cctcccacaa taaaggettc tcaatccgca
880

55

<210> 58

<211> 5532

<212> DNA

<213> Homo sapiens

<400> 58

gccgcgctgc gccggagtcc cgagctagcc ccggcgccgc cgccgcccag accggacgac 60

aggccacctc gtcggcgctcc gcccgagtcc ccgcctcgcc gccaacgcc caaccaccgc 120

gcacggcccc ctgactccgt ccagtattga tcgggagagc cggagcgagc tcttcgggga 180

gcagcgatgc gaccctccgg gacggccggg gcagcgctcc tggcgctgct ggctgcgctc 240

tgcccgcgca gtcgggctct ggaggaaaag aaagtttgcc aaggcacgag taacaagctc 300

acgcagttgg gcacttttga agatcatttt ctcagcctcc agaggatgtt caataactgt 360

gagggtgtcc ttgggaattt ggaaattacc tatgtgcaga ggaattatga tctttccttc 420

ttaaagacca tccaggaggt ggctggttat gtcctcattg ccctcaacac agtggagcga 480

attcctttgg aaaacctgca gatcatcaga ggaaatatgt actacgaaaa ttcctatgcc 540

ttagcagtct tatctaacta tgatgcaaat aaaaccggac tgaaggagct gcccatgaga 600

aatttacagg aaatcctgca tggcgccgtg cggttcagca acaaccctgc cctgtgcaac 660

gtggagagca tccagtggcg ggacatagtc agcagtgact ttctcagcaa catgtcgatg 720

gacttcaga accacctggg cagctgcaa aagtgtgatc caagctgtcc caatgggagc 780

tgctggggtg caggagagga gaactgccag aaactgacca aaatcatctg tgcccagcag 840

tgctccgggc gctgccgtgg caagtcccc agtgactgct gccacaacca gtgtgctgca 900

ggctgcacag gccccggga gagcgactgc ctggtctgcc gcaaattccg agacgaagcc 960

acgtgcaagg acacctgccc cccactcatg ctctacaacc ccaccacgta ccagatggat
1020

5 gtgaaccccg agggcaaata cagcttttgt gccacctgcg tgaagaagtg tccccgtaat
1080

tatgttgtga cagatcacgg ctctgtcgctc cgagcctgtg gggccgacag ctatgagatg
1140

10 gaggaagacg gcgtccgcaa gtgtaagaag tgcaaggggc cttgccgcaa agtgtgtaac
1200

ggaataggta ttggtgaatt taaagactca ctctccataa atgctacgaa tattaacac
1260

15 ttcaaaaact gcacctccat cagtggcgat ctccacatcc tgccggtggc atttaggggt
1320

gactccttca cacatactcc tcctctggat ccacaggaac tggatattct gaaaaccgta
1380

aaggaaatca cagggttttt gctgattcag gcttggcctg aaaacaggac ggacctccat
1440

25 gcctttgaga acctagaaat catagcggc aggaccaagc aacatggtca gttttctctt
1500

gcagtcgtca gcctgaacat aacatccttg ggattacgct ccctcaagga gataagtgat
1560

30 ggagatgtga taatttcagg aaacaaaaat ttgtgctatg caaatacaat aaactggaaa
1620

aaactgtttg ggacctccg tcagaaaacc aaaattataa gcaacagagg tgaaaacagc
1680

tgcaaggcca caggccaggc ctgccatgcc ttgtgetccc ccgagggctg ctggggcccg
1740

40 gagcccaggg actgctctc ttgccggaat gtcagccgag gcagggaatg cgtggacaag
1800

tgcaagcttc tggagggtga gccaaaggag ttgtggaga actctgagtg catacagtgc
1860

45 caccagagt gcctgcctca ggccatgaac atcacctgca caggacgggg accagacaac
1920

tgtatccagt gtgcccacta cattgacggc cccactgcg tcaagacctg cccggcagga
1980

50 gtcatgggag aaaacaacac cctggtctgg aagtacgcag acgccggcca tgtgtgccac
2040

ctgtgccatc caaactgcac ctacggatgc actgggccag gtcttgaagg ctgtccaacg
2100

aatgggccta agatcccgtc catcgccact gggatggtgg gggccctcct cttgctgctg
 2160
 5 gtggtggccc tggggatcgg cctcttcatg cgaaggcgcc acatcgttcg gaagcgcacg
 2220
 ctgcgaggc tgctgcagga gagggagctt gtggagcctc ttacaccag tggagaagct
 2280
 10 cccaaccaag ctctcttgag gatcttgaag gaaactgaat tcaaaaagat caaagtgctg
 2340
 ggctccggtg cgttcggcac ggtgtataag ggactctgga tcccagaagg tgagaaagtt
 2400
 15 aaaattcccg tcgctatcaa ggaattaaga gaagcaacat ctccgaaagc caacaaggaa
 2460
 atcctcgatg aagcctacgt gatggccagc gtggacaacc cccacgtgtg ccgcctgctg
 2520
 ggcactgcc tcacctccac cgtgcaactc atcacgcagc tcatgccctt cggctgcctc
 2580
 25 ctggactatg tccgggaaca caaagacaat attggctccc agtacctgct caactgggtg
 2640
 gtgcagatcg caaagggcat gaactacttg gaggaccgtc gcttggtgca ccgcgacctg
 2700
 30 gcagccagga acgtactggt gaaaacaccg cagcatgtca agatcacaga ttttgggctg
 2760
 gccaaactgc tgggtgcgga agagaaagaa taccatgcag aaggaggcaa agtgcctatc
 2820
 aagtggatgg cattggaatc aattttacac agaattctata cccaccagag tgatgtctgg
 2880
 40 agctacgggg tgaccgtttg ggagttgatg acctttggat ccaagccata tgacggaatc
 2940
 cctgccagcg agatctcctc catcctggag aaaggagaac gcctccctca gccaccata
 3000
 45 tgtaccatcg atgtctacat gatcatggtc aagtgtgga tgatagacgc agatagtgcg
 3060
 ccaaagttcc gtgagttgat catcgaattc tccaaaatgg cccgagacc cagcgctac
 3120
 cttgtcattc agggggatga aagaatgcat ttgccaagtc ctacagactc caacttctac
 3180
 55 cgtgccctga tggatgaaga agacatggac gacgtggtgg atgccgacga gtacctcatc
 3240

ccacagcagg gctttcttcag cagccctcc acgtcacgga ctccctctct gagctctctg
 3300

5 agtgcaacca gcaacaattc caccgtggct tgcattgata gaaatgggct gcaaagctgt
 3360

cccatcaagg aagacagctt cttgcagcga tacagctcag accccacagg cgccttgact
 3420

10 gaggacagca tagacgacac cttcctccca gtgcctgaat acataaacca gtccgttccc
 3480

aaaaggcccg ctggctctgt gcagaatcct gtctatcaca atcagcctct gaaccccgcg
 15 3540

cccagcagag acccacacta ccaggacccc cacagcactg cagtgggcaa ccccgagtat
 3600

20 ctcaacactg tccagcccac ctgtgtcaac agcacattcg acagccctgc ccactggggc
 3660

cagaaaggca gccaccaaatt tagcctggac aaccctgact accagcagga cttctttccc
 3720

25 aaggaagcca agccaaatgg catctttaag ggctccacag ctgaaaatgc agaataccta
 3780

agggctcgcgc cacaaagcag tgaatttatt ggagcatgac cacggaggat agtatgagcc
 30 3840

ctaaaaatcc agactctttc gatacccagg accaagccac agcaggctct ccatcccaac
 3900

35 agccatgccc gcattagctc ttagaccac agactgggtt tgcaacgttt acaccgacta
 3960

gccaggaagt acttccacct cgggcacatt ttgggaagtt gcattccttt gtcttcaaac
 4020

40 tgtgaagcat ttacagaaac gcatccagca agaattattgt ccctttgagc agaaatttat
 4080

ctttcaaaga ggtatatattg aaaaaaaaaa aaaaagtata tgtgaggatt tttattgatt
 4140

45 ggggatcttg gagtttttca ttgtcgctat tgatttttac ttcaatgggc tcttccaaca
 4200

aggaagaagc ttgctggtag cacttgctac cctgagttca tccaggccca actgtgagca
 50 4260

aggagcacia gccacaagtc ttccagagga tgcttgattc cagtggttct gcttcaaggc
 4320

55 ttccactgca aaacactaaa gatccaagaa ggccttcatg gcccagcag gccggatcgg
 4380

tactgtatca agtcatggca ggtacagtag gataagccac tctgtccctt cctgggcaaa
4440

5 gaagaaacgg aggggatgaa ttcttcctta gacttacttt tgtaaaaatg tccccacggt
4500

acttactccc cactgatgga ccagtggttt ccagtcata gcgtagact gacttgtttg
4560

10 tcttccattc cattgttttg aaactcagta tgccgcccct gtcttgctgt catgaaatca
4620

gcaagagagg atgacacatc aaataataac tcggattcca gccacattg gattcatcag
15 4680

catttgacc aatagccac agctgagaat gtggaatacc taaggataac accgcttttg
4740

20 ttctcgcaaa aacgtatctc ctaatttgag gctcagatga aatgcatcag gtcctttggg
4800

gcatagatca gaagactaca aaaatgaagc tgctctgaaa tctcctttag ccatcacccc
4860

25 aaccccccaa aattagtttg tgttacttat ggaagatagt tttctccttt tacttcactt
4920

caaaagcttt ttactcaaag agtatatgtt cctccaggt cagctgcccc caaacccctt
30 4980

ccttacgctt tgtcacacaa aaagtgtctc tgcttgagt catctattca agcaattaca
5040

35 gctctggcca caacagggca ttttacaggt gcgaatgaca gtagcattat gagtagtgtg
5100

aattcaggta gtaaataatga aactaggggt tgaaattgat aatgctttca caacatttgc
5160

40 agatgtttta gaaggaaaaa agttccttcc taaaataatt tctctacaat tggaagattg
5220

gaagattcag ctagttagga gcccatTTTT tcctaattctg tgtgtgccct gtaacctgac
45 5280

tggttaacag cagtcctttg taaacagtgt tttaaactct cctagtcaat atccacccca
5340

50 tccaatttat caaggaagaa atgggttcaga aaatatTTTc agcctacagt tatgttcagt
5400

cacacacaca tacaaaatgt tccttttgct tttaaagtaa ttttgactc ccagatcagt
5460

55 cagagcccct acagcattgt taagaaagta ttgattttt gtctcaatga aaataaaact
5520

atattcattt cc
5532

5

10

<210> 59

<211> 4530

15

<212> DNA

<213> Homo sapiens

20

<400> 59

aattctcgag ctgctcgacc ggtcgacgag ctcgagggtc gacgagctcg agggcgcgcg 60

25

cccgccccc acccctcgca gcaccccgcg ccccgcgccc tcccagccgg gtccagccgg
120

agccatgggg ccggagccgc agtgagcacc atggagctgg cggccttggt cgcctggggg
180

30

ctcctcctcg ccctcttgcc ccccgagacc gcgagcacc aagtgtgcac cggcacagac
240

atgaagctgc ggctccctgc cagtcccgag acccactgg acatgctccg ccacctctac
300

35

cagggtgcc aggtggtgca gggaaacctg gaactcacct acctgccac caatgccagc
360

ctgtccttcc tgcaggatat ccaggaggtg cagggtacg tgctcatcgc tcacaaccaa
420

40

gtgaggcagg tccactgca gaggtgcgg attgtgcgag gcaccagct ctttgaggac
480

45

aactatgcc tggccgtgct agacaatgga gaccgctga acaataccac cctgtcaca
540

ggggcctccc caggaggcct gcgggagctg cagcttcgaa gcctcacaga gatcttgaaa
600

50

ggaggggtct tgatccagcg gaacccccag ctctgctacc aggacacgat tttgtggaag
660

55

gacatcttcc acaagaacaa ccagctggct ctcacactga tagacaccaa ccgctctcgg
720

gcctgccacc cctgttctcc gatgtgtaag ggctcccgt gctggggaga gagttctgag
780

5 gattgtcaga gcctgacgcg cactgtctgt gccggtggct gtgcccgtg caaggggcca
840

ctgccactg actgctgcca tgagcagtgt gctgccggt gcacggggccc caagcactct
900

10 gactgcctgg cctgcctcca cttcaaccac agtggcatct gtgagctgca ctgccagcc
960

ctggtcacct acaacacaga cacgtttgag tccatgccca atcccaggag cgggtataca
1020

15 ttccggcgcca gctgtgtgac tgcctgtccc tacaactacc tttctacgga cgtgggatcc
1080

tgcaccctcg tctgccccct gcacaaccaa gaggtgacag cagaggatgg aacacagcgg
1140

tgtgagaagt gcagcaagcc ctgtgcccg gtgtgctatg gtctgggcat ggagcacttg
1200

25 cgagaggatga gggcagttac cagtgccaat atccaggagt ttgctggctg caagaagatc
1260

tttgggagcc tggcatttct gccggagagc tttgatgggg acccagcctc caacactgcc
1320

30 ccgctccagc cagagcagct ccaagtgttt gagactctgg aagagatcac aggttaccta
1380

tacatctcag catggccgga cagcctgcct gacctcagcg tcttcagaa cctgcaagta
1440

atccggggac gaattctgca caatggcgcc tactcgctga ccctgcaagg gctgggcatc
1500

40 agctggctgg ggctgcgctc actgagggaa ctgggcagt gactggccct catccaccat
1560

aacaccacc tctgcttctg gcacacgggt ccctgggacc agctctttcg gaaccgcac
1620

45 caagctctgc tccacactgc caaccggcca gaggacgagt gtgtgggcca gggcctggcc
1680

tgccaccagc tgtgcgccc agggcactgc tggggtccag ggcccacca gtgtgtcaac
1740

tgacgccagt tccttcgggg ccaggagtgc gtggaggaat gccgagtact gcaggggctc
1800

55 cccagggagt atgtgaatgc caggcactgt ttgccgtgcc accctgagtg tcagccccag
1860

aatggctcag tgacctgttt tggaccggag gctgaccagt gtgtggcctg tgcccactat
 1920

5 aaggaccctc ccttctgcgt ggcccgcgtc cccagcgggtg tgaaacctga cctctcctac
 1980

atgcccatct ggaagtttcc agatgaggag ggcgcattgc agccttgccc catcaactgc
 2040

10 acccactcct gtgtggacct ggatgacaag ggctgccccg ccgagcagag agccagccct
 2100

ctgacgtcca tcgtctctgc ggtggttggc attctgctgg tcgtggtctt gggggtggtc
 15 2160

tttgggatcc tcatcaagcg acggcagcag aagatccgga agtacacgat gcggagactg
 2220

20 ctgcaggaaa cggagctggt ggagccgctg acacctagcg gagcgatgcc caaccaggcg
 2280

cagatgcgga tcctgaaaga gacggagctg aggaaggtga aggtgcttgg atctggcgct
 2340

25 tttggcacag tctacaaggg catctggatc cctgatgggg agaattgtga aattccagtg
 2400

gccatcaaag tgttgaggga aaacacatcc ccaaagcca acaaagaaat cttagacgaa
 30 2460

gcatacgtga tggctggtgt gggctcccca tatgtctccc gccttctggg catctgcctg
 2520

35 acatccacgg tgcaagctgt gacacagctt atgccctatg gctgcctctt agaccatgtc
 2580

cgggaaaacc gcggacgctt gggctcccag gacctgctga actggtgtat gcagattgcc
 2640

40 aaggggatga gctacctgga ggatgtgcgg ctcgtacaca gggacttggc cgctcggaac
 2700

gtgctggtca agagtcccaa ccatgtcaaa attacagact tcgggctggc tcggctgctg
 45 2760

gacattgacg agacagagta ccatgcagat gggggcaagg tgcccatcaa gtggatggcg
 2820

50 ctggagtcca ttctccgccg gcggttcacc caccagagtg atgtgtggag ttatggtgtg
 2880

actgtgtggg agctgatgac ttttggggcc aaaccttacg atgggatccc agcccgggag
 2940

55 atccctgacc tgctggaaaa gggggagcgg ctgccccagc ccccatctg caccattgat
 3000

gtctacatga tcatgggtcaa atgttggatg attgactctg aatgtcggcc aagattccgg
3060

5 gagttggtgt ctgaattctc ccgcatggcc agggaccccc agcgctttgt ggtcatccag
3120

aatgaggact tgggcccagc cagtcccttg gacagcacct tctaccgctc actgctggag
3180

10 gacgatgaca tgggggacct ggtggatgct gaggagtatc tggtagccca gcagggcttc
3240

ttctgtccag accctgcccc gggcgctggg ggcatgggcc accacaggca ccgcagctca
3300

15 tctaccagga gtggcgggtg ggacctgaca ctagggctgg agccctctga agaggaggcc
3360

cccaggtctc cactggcacc ctccgaaggg gctggctccg atgtatttga tggtagcctg
3420

ggaatggggg cagccaaggg gctgcaaagc ctccccacac atgaccccag ccctctacag
3480

25 cggtacagtg aggaccccac agtacccttg ccctctgaga ctgatggcta cgttgcccc
3540

ctgacctgca gccccagcc tgaatatgtg aaccagccag atgttcggcc ccagcccct
3600

30 tgcgcccgag agggccctct gcctgctgcc cgacctgctg gtgccactct ggaaagggcc
3660

aagactctct cccagggaa gaatggggtc gtcaaagacg tttttgcctt tgggggtgcc
3720

gtggagaacc ccgagtactt gacaccccag ggaggagctg ccctcagcc ccaccctct
3780

40 cctgccttca gccagcctt cgacaacctc tattactggg accaggaccc accagagcgg
3840

ggggctccac ccagcacctt caaagggaca cctacggcag agaaccaga gtacctgggt
3900

45 ctggacgtgc cagtgtgaac cagaaggcca agtccgcaga agccctgatg tgtcctcagg
3960

gagcagggaa ggcctgactt ctgctggcat caagaggtgg gagggccctc cgaccacttc
4020

cagggaacc tgccatgcca ggaacctgtc ctaaggaaacc ttccttcctg cttgagttcc
4080

55 cagatggctg gaaggggtcc agcctcgttg gaagaggaac agcactgggg agtctttgtg
4140

gattctgagg ccctgcccaa tgagactcta ggggccagtg gatgccacag cccagcttgg
 4200

5 cccttttcctt ccagatcctg ggtactgaaa gccttaggga agctggcctg agaggggaag
 4260

cggccctaag ggagtgtcta agaacaaaag cgacccattc agagactgtc cctgaaacct
 4320

10 agtactgccc cccatgagga aggaacagca atggtgtcag tatccaggtt ttgtacagag
 4380

15 tgcttttctg tttagttttt actttttttg tttgtttttt ttaaagacga aataaagacc
 4440

caggggagaa tgggtgttgt atggggaggc aagtgtgggg ggtccttctc cacacccact
 4500

20 ttgtccattt gcaaataatat tttggaaaac
 4530

25 <210> 60
 <211> 801
 <212> DNA

30 <213> Homo sapiens

35 <400> 60
 caccgcaccc tcggactgcc ccaaggcccc cgccgccgct ccagcgccgc gcagccaccg 60
 ccgccgccgc cgcctctcct tagtcgccgc catgacgacc gcgtccacct cgcaggtgcg
 120

40 ccagaactac caccaggact cagaggccgc catcaaccgc cagatcaacc tggagctcta
 180

45 cgcctcttac gtttacctgt ccatgtctta ctactttgac cgcgatgatg tggctttgaa
 240

gaactttgcc aaatactttc ttcaccaatc tcatgaggag agggaacatg ctgagaaact
 300

50 gatgaagctg cagaaccaac gaggtggccg aatcttcctt caggatatca agaaaccaga
 360

ctgtgatgac tgggagagcg ggctgaatgc aatggagtgt gcattacatt tggaaaaaaa
 420

55

tgtgaatcag tcactactgg aactgcacaa actggccact gacaaaaatg acccccattt
 480

5 gtgtgacttc attgagacac attacctgaa tgagcagggtg aaagccatca aagaattggg
 540

tgaccacgtg accaacttgc gcaagatggg agcgcccgaa tctggcttgg cggaatatct
 600

10 ctttgacaag cacacctggg agacagtgat aatgaaagct aagcctcggg ctaatttccc
 660

atagccgtgg ggtgacttcc tggtcaccaa ggcagtgcac gcatgttggg gtttccttta
 720

15 ccttttctat aagttgtacc aaaacatcca ctttaagttct ttgatttgta ccattccttc
 780

20 aaataaagaa atttggtagc c
 801

25 <210> 61
 <211> 878
 <212> DNA

30 <213> Homo sapiens

35 <400> 61

gtcccgcggt tctgtctctt gcttcaacag tgtttggacg gaacagatcc ggggactctc 60

ttccagcctc cgaccgcct cagatttctc ctccgcttgc aacctccggg accatcttct
 120

40 cggccatctc ctgcttctgg gacctgccag caccgttttt gtggttagct ccttcttgcc
 180

aaccaaccat gagctcccag attcgtcaga attattccac cgacgtggag gcagccgtca
 240

45 acagcctggc caatttgtac ctgcaggcct cctacaccta cctctctctg ggcttctatt
 300

50 tcgaccgaga tgatgtggct ctggaaggcg tgagccactt cttccgcgaa ttggccgagg
 360

agaagcgaga gggctacgag cgtctcctga agatgcaaaa ccagcgtggc ggccgcgctc
 420

55

tcttccagga catcaagaag ccagctgaag atgagtgggg taaaacccca gacgccatga
480

5 aagctgccat ggccctggag aaaaagctga accaggccct tttggatctt catgccctgg
540

gttctgcccg cacggacccc catctctgtg acttcctgga gactcacttc ctagatgagg
600

10 aagtgaagct tatcaagaag atgggtgacc acctgaccaa cctccacagg ctgggtggcc
660

cggaggctgg gctgggcgag tatctcttcg aaaggctcac tctcaagcac gactaagagc
720

15 cttctgagcc cagcgacttc tgaagggcc cttgcaaagt aatagggtt ctgcctaagc
780

20 ctctccctcc agccaatagg cagctttctt aactatccta acaagccttg gaccaaattg
840

aaataaagct ttttgatgca aaaaaaaaaa aaaaaaaaaa
878

25

<210> 62

30 <211> 2747

<212> DNA

<213> Homo sapiens

35

<400> 62

40 catactccat gccagaatt cctgectcgc cactgtcctg ctgccctcca gacatgctgg 60

ggccctgcat gctgctgctg ctgctgctgc tgggcctgag gctacagctc tccctgggca
120

45 tcctcctagt tgaggaggag aaccgggact tctggaaccg cgaggcagcc gaggccttgg
180

gtgccgcaa gaagctgcag cctgcacaga cagccgcaa gaacctcatc atcttcctgg
240

50 gcgatgggat ggggtgtct acggtgacag ctgccaggat cctaaaaggg cagaagaagg
300

acaaactggg gcctgagata cccctggcca tggaccgtt cccatatgtg gctctgtcca
360

55

agacatacaa thtagacaaa catgtgccag acagtggagc cacagccacg gcctacctgt
420

5 gcgggggtcaa gggcaacttc cagaccattg gcttgagtgc agccgcccgc tttaccagt
480

gcaacacgac acgcggaac gaggtcatct ccgtgatgaa tcgggccaag aaagcaggga
540

10 agtcagtggg agtggtaacc accacacgag tgacgacgc ctgccagcc ggcacctacg
600

ccacacggt gaaccgcaac tggactcgg acgccgacgt gcctgcctcg gcccgccagg
15 660

aggggtgcca ggacatcgct acgcagctca tctccaacat ggacattgac gtgatcctag
720

20 gtgggggccc aaagtacatg tttcgcatgg gaaccccaga ccctgagtac ccagatgact
780

acagccaagg tgggaccagg ctggacggga agaactctgt gcaggaatgg ctggcgaagc
840

25 gccagggtgc ccggtacgtg tggaaccgca ctgagctcat gcaggcttcc ctggaccgt
900

ctgtggccca tctcatgggt ctctttgagc ctggagacat gaaatacgag atccaccgag
30 960

actccacact ggacccctcc ctgatggaga tgacagaggc tgccctgcgc ctgctgagca
1020

35 ggaacccccg cggtttcttc ctcttcgtgg aggggtggtcg catcgacat ggtcatcatg
1080

aaagcagggc ttaccgggca ctgactgaga cgatcatgtt cgacgacgcc attgagaggg
1140

40 cgggccagct caccagcgag gaggacacgc tgagcctcgt cactgccgac cactcccag
1200

tcttctcctt cggaggctac cccctgcgag ggagctccat cttcgggctg gccctggca
45 1260

agggccggga caggaaggcc tacacggtcc tcctatacgg aaacggtcca ggctatgtgc
1320

50 tcaaggacgg cggccggccg gatgttaccg agagcgagag cgggagcccc gagtatcggc
1380

agcagtcagc agtggccctg gacgaagaga cccacgcagg cgaggacgtg gcgggtgttcg
1440

55 cgcgcggccc gcaggcgac ctggttcacg gcgtgcagga gcagacctc atagcgacg
1500

tcatggcctt cgccgcctgc ctggagccct acaccgctg cgacctggcg cccccgcgg
 1560

5 gcaccaccga cgccgcgcac ccggggcggt ccgtgggcc ccggttgctt cctctgctgg
 1620

ccgggaccct gctgctgctg gagacggcca ctgctccctg agtgtcccg cctgggggt.
 1680

10 cctgcttccc catcccgag ttctcctgt ccccgctcc tgtcgtcctg cctggcctcc
 1740

agcccgagtc gtcaccccg gagtcctat acagaggcc tgccatggaa ccttccctc
 1800

15 cccgtgcgt ctggggactg agcccatgac accaaacctg ccccttgggt gctctcggac
 1860

20 tccctacccc aacccaggg actgcaggt gtgccctgtg gctgcctgca cccaggaaa
 1920

ggagggggct caggccatcc agccaccacc tacagcccag tgggtaccag gcaggctccc
 1980

25 ttcttgggga aaagaagcac ccagaccgg cgccccgctg atctttgctt cagtccttga
 2040

atcacctgtg ggacttgagg actcgggatc ttcaggacgc ctggagaagg gtggtttcct
 2100

30 gccaccctgc tggccaagga ggctcctgg gtggggatca ccagggggat tttgacacag
 2160

ccttcggctg cccccacta agttaattcc acaccctgt acccccagg gggccctctg
 2220

35 cctcatggca aaggcttgcc ccaaattca acttctcaga cgttcatac cccacatgc
 2280

40 caatttcagc acccaactga gatccgagga gctcctggga agcctgggt gcaggacact
 2340

ggtcgagagc caaaggtccc tccccagaca tctggacact gggcatagat ttctcaagaa
 2400

45 ggaagactcc cctgcctccc cagggcctct gctctcctgg gagacaaagc aataataaaa
 2460

ggaagtgttt gtaatccag cactttggga ggccgaggtg ggcggatcac gaggtcagga
 2520

50 gatggagacc atcctggcta acacgtgaa accccttata tatgcgctg tagtcccagc
 2580

55 taccaggag gctgaagcag gataatcgt tgaaccggg cgccggagat tgcagtgagc
 2640

EP 1 439 393 A2

cgaggtcatg ccactgcact gcagcctggg cgacagagcg agattctgcc tcaaaaataa
2700

5 acaaataaat tttaaaaata aataaataat aaaaggaagt gtttagac
2747

10 <210> 63
<211> 2062
<212> DNA

15 <213> Homo sapiens

20 <400> 63
gtcagtcctt cctgtagccg ccgcccgcgc cgcccgcgc ccctctgccg gcagctccgg 60
cgccacctcg ggccggcgtc tccggcgggc gggagccagg cgctgacggg cgcggcgggg
25 120
gcggccgagc gctcctgcgg ctgcgactca ggctccggcg tctgcgcttc cccatggggc
180
tggcctgcgg cgccctggcg ctctgagatt gtcactgctg ttccaagggc acacgcagag
30 240
ggatttgga ttcctggaga gttgcctttg tgagaagctg gaaatatttc tttcaattcc
300
35 atctcttagt tttccatagg aacatcaaga aatcatgaac aactttggta atgaagagtt
360
tgactgccac ttcctcgatg aagggtttac tgccaaggac attctggacc agaaaattaa
40 420
tgaagtttct tcttctgatg ataaggatgc cttctatgtg gcagacctgg gagacattct
480
aaagaaacat ctgaggtggt taaaagctct ccctcgtgtc accccctttt atgcagtcaa
45 540
atgtaatgat agcaaagcca tcgtgaagac cttgctgct accgggacag gatttgactg
600
50 tgctagcaag actgaaatac agttggtgca gactctgggg gtgcctccag agaggattat
660
ctatgcaa at ccttgtaa ac aagtatctca aattaagtat gctgctaata atggagtcca
720
55

gatgatgact tttgatagtg aagttgagtt gatgaaagtt gccagagcac atcccaaagc
 780
 5 aaagttggtt ttgcggattg ccactgatga ttccaaagca gtctgtcgtc tcagtgtgaa
 840
 attcgtgccc acgctcagaa ccagcaggct ccttttgga .cgggcgaaag agctaaatat
 900
 10 cgatgttggtt ggtgtcagct tccatgtagg aagcggctgt accgatcctg agaccttcgt
 960
 gcaggcaatc tctgatgccc gctgtgtttt tgacatgggg gctgaggttg gtttcagcat
 15 1020
 gtatctgctt gatattggcg gtggctttcc tggatctgag gatgtgaaac ttaaatttga
 1080
 20 agagatcacc ggcgtaatca acccagcgtt ggacaaatac tttccgtcag actctggagt
 1140
 gagaatcata gctgagcccg gcagatacta tgttgcatca gctttcacgc ttgcagttaa
 1200
 25 tatcattgcc aagaaaattg tattaagga acagacgggc tctgatgacg aagatgagtc
 1260
 gagtgagcag acctttatgt attatgtgaa tgatggcgtc tatggatcat ttaattgcat
 30 1320
 actctatgac cacgcacatg taaagcccct tctgcaaaag agacctaaac cagatgagaa
 1380
 35 gtattattca tccagcatat ggggaccaac atgtgatggc ctcgatcga ttgttgagcg
 1440
 ctgtgacctg cctgaaatgc atgtgggtga ttggatgctc tttgaaaaca tgggcgctta
 1500
 40 cactgttgct gctgcctcta cgttcaatgg cttccagagg ccgacgatct actatgtgat
 1560
 gtcagggcct gcgtggcaac tcatgcagca attccagaac cccgacttcc caccgaagt
 1620
 45 agaggaacag gatgccagca ccctgcctgt gtcttggtgcc tgggagagtg ggatgaaacg
 1680
 ccacagagca gcctgtgctt cggctagtat taatgtgtag atagcactct ggtagctgtt
 50 1740
 aactgcaagt ttagcttgaa ttaagggatt tggggggacc atgtaactta attactgcta
 1800
 55 gttttgaaat gtctttgtaa gagtagggtc gccatgatgc agccatatgg aagactagga
 1860

EP 1 439 393 A2

tatgggtcac acttatctgt gttcctatgg aaactatttg aatatttggt ttatatggat
1920

5 ttttattcac tcttcagaca cgctactcaa gagtgcccct cagctgctga acaagcattt
1980

gtagcttgta caatggcaga atgggcctaa agcttagtgt tgtgacctgt ttttaaata
2040

10 aagtatcttg aaataattag gc
2062

15 <210> 64

<211> 3557

20 <212> DNA

<213> Homo sapiens

25 <400> 64

gagaggggtcc ttcaggggtct gcttatgccc ttgttcaaga acaccagtgt cagctctctg 60

30 tactctgggt gcagactgac cttgctcagg cctgagaagg atggggcagc caccagagt
120

gatgctgtct gcacccatcg tcctgacccc aaaagccctg gactggacag agagcggctg
180

35 tactggaagc tgagccagct gacccacggc atcactgagc tggggcccta caccctggac
240

aggcacagtc tctatgtcaa tggtttcacc catcagagct ctatgacgac caccagaact
300

40 cctgatacct ccacaatgca cctggcaacc tcgagaactc cagcctccct gtctggacct
360

acgaccgcca gccctctcct ggtgctattc acaattaact tcaccatcac taacctgcgg
420

45 tatgaggaga acatgcatca ccctggctct agaaagtta acaccacgga gagagtcctt
480

50 caggggtctgc tcaggcctgt gttcaagaac accagtgttg gccctctgta ctctggctgc
540

agactgacct tgctcaggcc caagaaggat ggggcagcca ccaaagtgga tgccatctgc
600

55

acctaccgcc ctgatcccaa aagccctgga ctggacagag agcagctata ctgggagctg
 660
 5 agccagctaa cccacagcat cactgagctg ggccctaca ccctggacag ggacagtctc
 720
 tatgtcaatg gtttcacaca gcggagctct gtgcccacca ctagcattcc tgggaccccc
 780
 10 acagtggacc tgggaacatc tgggactcca gtttctaaac ctgggtccctc ggctgccagc
 840
 cctctcctgg tgctattcac tctcaacttc accatcacca acctgcggtg tgaggagaac
 900
 15 atgcagcacc ctggctccag gaagtccaac accacggaga gggtccttca gggcctgctc
 960
 aggtccctgt tcaagagcac cagtgttggc cctctgtact ctggctgcag actgactttg
 1020
 ctcaggcctg aaaaggatgg gacagccact ggagtggatg ccatctgcac ccaccacct
 1080
 25 gaccccaaaa gccctaggct ggacagagag cagctgtatt gggagctgag ccagctgacc
 1140
 cacaatatca ctgagctggg ccactatgcc ctggacaacg acagcctctt tgtcaatggt
 1200
 30 ttcactcatc ggagctctgt gtccaccacc agcactcctg ggacccccac agtgtatctg
 1260
 ggagcatcta agactccagc ctcgatattt ggcccttcag ctgccagcca tctcctgata
 1320
 35 ctattcacc ctaacttcac catcactaac ctgcggtatg aggagaacat gtggcctggc
 1380
 40 tccaggaagt tcaacactac agagaggggc cttcagggcc tgctaaggcc cttgttcaag
 1440
 aacaccagtg ttggccctct gtactctggc tccaggctga ccttgctcag gccagagaaa
 1500
 45 gatggggaag ccaccggagt ggatgccatc tgcaccacc gccctgaccc cacaggccct
 1560
 gggctggaca gagagcagct gtatttggag ctgagccagc tgaccacag catcactgag
 1620
 50 ctgggcccct acacactgga caggacagct ctctatgtca atggtttcac ccacggagc
 1680
 55 tctgtaccca ccaccagcac cgggggtggc agcgaggagc cattcacact gaacttcacc
 1740

atcaacaacc tgcgtacat ggcggacatg ggccaacccg gctccctcaa gttcaacatc
 1800
 5 acagacaacg tcatgaagca cctgctcagt cctttgttcc agaggagcag cctgggtgca
 1860
 cggtagacag gctgcagggc catcgacta aggtctgtga agaacgggtgc tgagacacgg
 1920
 10 gtggacctcc tctgcaccta cctgcagccc ctacagggcc caggtctgcc tatcaagcag
 1980
 gtgttccatg agctgagcca gcagacccat ggcatcaccg ggctggggcc ctactctctg
 2040
 15 gacaaagaca gcctctacct taacggttac aatgaacctg gtctagatga gcctcctaca
 2100
 20 actcccaagc cagccaccac attcctgcct cctctgtcag aagccacaac agccatgggg
 2160
 taccacctga agaccctcac actcaacttc accatctcca atctccagta ttcaccagat
 2220
 25 atgggcaagg gctcagctac attcaactcc accgaggggg tccttcagca cctgctcaga
 2280
 cccttgttcc agaagagcag catggggccc ttctacttgg gttgccaact gatctccctc
 2340
 30 aggcctgaga aggatggggc agccactggt gtggacacca cctgcaccta ccacctgac
 2400
 35 cctgtggggc ccgggctgga catacagcag ctttactggg agctgagtca gctgacccat
 2460
 ggtgtcaccg aactgggctt ctatgtcctg gacagggata gcctcttcat caatggctat
 2520
 40 gcaccccgaga atttatcaat ccggggcgag taccagataa atttcacat tgtcaactgg
 2580
 aacctcagta atccagaccc cacatcctca gagtacatca ccctgctgag ggacatccag
 2640
 45 gacaaggatc ccacactcta caaaggcagt caactacatg acacattccg cttctgcctg
 2700
 gtcaccaact tgacgatgga ctccgtgttg gtcactgtca aggcattgtt ctctccaat
 2760
 50 ttggacccca gcctgggtgga gcaagtcttt ctagataaga ccctgaatgc ctcatccat
 2820
 55 tggctgggct ccacctacca gttggtggac atccatgtga cagaaatgga gtcacatgtt
 2880

tatcaaccaa caagcagctc cagcaccag cacttctacc cgaatttcac catcaccaac
 2940
 5 ctaccatatt cccaggacaa agcccagcca ggcaccacca attaccagag gaacaaaagg
 3000
 aatattgagg atgcgctcaa ccaactcttc cgaaacagca gcatcaagag ttatTTTTct
 3060
 10 gactgtcaag tttcaacatt caggctctgtc cccaacaggc accacaccgg ggtggactcc
 3120
 ctgtgtaact tctcgccact ggctcggaga gtagacagag ttgccatcta tgaggaattt
 15 3180
 ctgcggatga cccggaatgg taccagctg cagaacttca ccctggacag gagcagtgtc
 3240
 20 cttgtggatg ggtattctcc caacagaaat gagcccttaa ctgggaattc tgaccttccc
 3300
 ttctgggctg tcattctcat cggcttgga ggactcctgg gactcatcac atgcctgac
 3360
 25 tgcggtgtcc tggtgaccac ccgccggcgg aagaaggaag gagaatacaa cgtccagcaa
 3420
 cagtgccag gctactacca gtcacaccta gacctggagg atctgcaatg actggaactt
 30 3480
 gccggtgcct ggggtgcctt tccccagcc agggtcctaaa gaagcttggc tggggcagaa
 3540
 35 ataaaccata ttggtcg
 3557
 40 <210> 65
 <211> 3464
 <212> DNA
 45 <213> Homo sapiens
 <400> 65
 50 cagccgtgct cgaagcgttc ctggagccca agctctctc cacaggtgaa gacagggcca 60
 gcaggagaca ccatggggca cctctcagcc cacttcaca gagtgcgtgt accctggcag
 120
 55

gggcttctgc tcacagcctc acttctaacc ttctggaacc cgcccaccac tgcccagctc
 180
 5 actactgaat ccatgccatt caatgttgca gaggggaagg aggttcttct ccttgtccac
 240
 aatctgcccc agcaactttt tggctacagc tggtaaaaag gggaaagagt ggatggcaac
 300
 10 cgtcaaattg taggatatgc aataggaact caacaagcta cccaggggc cgcaaacagc
 360
 ggtcgagaga caatataccc caatgcatcc ctgctgatcc agaacgtcac ccagaatgac
 420
 15 acaggattct acaccctaca agtcataaag tcagatcttg tgaatgaaga agcaactgga
 480
 20 cagttccatg tatacccgga gctgccaag cctccatct ccagcaaca ctccaaccct
 540
 gtggaggaca aggatgctgt ggccttcacc tgtgaacctg agactcagga cacaacctac
 600
 25 ctgtggtgga taaacaatca gagcctcccg gtcagtccca ggctgcagct gtccaatggc
 660
 aacaggaccc tcactctact cagtgtcaca aggaatgaca caggacccta tgagtgtgaa
 720
 30 atacagaacc cagtgagtgc gaaccgcagt gaccagtc cttggaatgt cacctatggc
 780
 ccggacaccc ccaccatttc cccttcagac acctattacc gtccaggggc aaacctcagc
 840
 ctctcctgct atgcagcctc taaccacct gcacagtact cctggcttat caatggaaca
 900
 40 ttccagcaaa gcacacaaga gctctttatc cctaacaatca ctgtgaataa tagtggatcc
 960
 tatacctgcc acgccaataa ctcagtcact ggctgcaaca ggaccacagt caagacgatc
 1020
 45 atagtcactg agctaagtcc agtagtagca aagcccaaaa tcaaagccag caagaccaca
 1080
 gtcacaggag ataaggactc tgtgaacctg acctgctcca caaatgacac tggaatctcc
 1140
 50 atccgttggt tcttcaaaaa ccagagtctc ccgtcctcgg agaggatgaa gctgtcccag
 1200
 55 ggcaacacca cctcagcat aaacctgtc aagagggagg atgctgggac gtattggtgt
 1260

gaggtcttca acccaatcag taagaaccaa agcgacccca tcatgctgaa cgtaaactat
1320

5 aatgctctac cacaagaaaa tggcctctca cctggggcca ttgctggcat tgtgattgga
1380

gtagtgcccc tggttgctct gatagcagta gccctggcat gttttctgca tttcgggaag
1440

10 accggcaggg caagcgacca gcgtgatctc acagagcaca aaccctcagt ctccaaccac
1500

actcaggacc actccaatga ccacacctaac aagatgaatg aagttactta ttctaccctg
1560

15 aactttgaag cccagcaacc cacacaacca acttcagcct ccccatccct aacagccaca
1620

20 gaaataatth attcagaagt aaaaaagcag taatgaaacc tgtcctgctc actgcagtgc
1680

tgatgtatth caagtctctc accctcatca ctaggagatt cctttcccct ctagggtaga
1740

25 ggggtgggga cagaaacaac tttctctac tcttccttcc taataggcat ctccaggctg
1800

cctggctact gccctctctc cagtgtcaat agatgaaagt acattgggag tctgtaggaa
1860

30 acccaacctt cttgtcattg aaatttggca aagctgactt tgggaaagag ggaccagaac
1920

35 ttcccctccc ttcccctttt cccaacctgg acttgthtta aactgcctg ttcagagcac
1980

tcattccttc ccacccccag tctgtccta tcaacttaat tcggatttgc catagccttg
2040

40 aggttatgtc cttttccatt aagtacatgt gccaggaaac agcgagagag agaaagtaaa
2100

cggcagtaat gcttctccta tttctccaaa gccttggtg aactagcaaa gagaagaaaa
2160

45 ccaaataat aaccaatagt gaaatgccac aggtttgtcc actgtcaggg ttgtctacct
2220

gtaggatcag ggtctaagca ccttggtgct tagctagaat accacctaact ccttctggca
2280

50 agcctgtctt cagagaaccc actagaagca actaggaaaa atcacttgcc aaaatccaag
2340

55 gcaattcctg atggaaaatg caaaagcaca tatatgtttt aatatcttta tgggctctgt
2400

tcaaggcagt gctgagaggg aggggttata gcttcaggag ggaaccagct tctgataaac
2460

5 acaatctgct aggaacttgg gaaaggaatc agagagctgc ccttcagcga ttattttaa
2520

tattgttaaa gaatacaca tttgggggat tgggattttt ctctttttct ctgagacatt
2580

10 ccaccatttt aatttttgta actgcttatt tatgtgaaaa gggttatttt tacttagctt
2640

agctatgtca gccaatccga ttgccttagg tgaaagaaac caccgaaatc cctcagggtcc
15 2700

cttggtcagg agcctctcaa gatttttttt gtcagaggct ccaaatagaa aataagaaaa
2760

20 ggttttcttc attcatggct agagctagat ttaactcagt ttctaggcac ctgagaccaa
2820

tcatcaacta ccattctatt ccatgtttgc acctgtgcat tttctgtttg cccccattca
2880

25 ctttgtcagg aaaccttggc ctctgctaag gtgtatttgg tccttgagaa gtgggagcac
2940

cctacagga cactatcact catgctgggt gcattgttta cagctagaaa gctgcactgg
3000

30 tgctaatagcc ccttgggaaa tggggctgtg aggaggagga ttataactta ggctagcct
3060

cttttaacag cctctgaaat ttatcttttc ttctatgggg ottataaatg tatcttataa
35 3120

taaaaaggaa ggacaggagg aagacaggca aatgtacttc tcaccagtc ttctacacag
3180

40 atggaatctc tttggggcta agagaaaggt tttattctat attgcttacc tgatctcatg
3240

ttaggcctaa gaggctttct ccaggaggat tagcttggag ttctctatac tcaggtaacct
3300

45 ctttcagggt tttctaacc tgacacggac tgtgcatact ttccctcatc catgctgtgc
3360

tgtgttattt aatttttctt ggctaagatc atgtctgaat tatgtatgaa aattattcta
50 3420

tgtttttata ataaaaataa tatatcagac atcgaaaaaa aaaa
3464

55

<210> 66
 <211> 1022
 5 <212> DNA
 <213> Homo sapiens
 10
 <400> 66
 tcctggagcc caggctcttt tccacagagg aggaaagagc aggcagcaga gaccatgggg 60
 15 cccccctcag cccctcccca cagagaatgc atcccctggc aggggcttct gctcacagcc
 120
 tcacttctaa acttctggaa cccgcccacc actgccaagc tcactattga atccatgccg
 20 180
 ctcaagtgtcg cagaggggaa ggaggtgctt ctacttgtcc acaatctgcc ccagcatctt
 240
 tttggctaca gctggtacaa aggggaaaga gtggatggca acagtctaata tgtgggatat
 25 300
 gtaataggaa ctcaacaagc taccacaggg gccgcataca gcggtcgaga gacaatatac
 360
 30 accaatgcat ccctgctgat ccagaatgtc acccagaatg acataggatt ctacacccta
 420
 caagtcataa agtcagatct tgtgaatgaa gaagcaactg gacagttcca tgtataccaa
 480
 35 gaaaatgccc caggccttcc tgtggggggcc gtgcgccgga tcgtgaccgg ggtcctggtc
 540
 ggagtggcgc tgggtggccgc gctggtgtgt ttctgtctcc ttgccaaaac tggaaggccg
 40 600
 ttgtccctcc cacagctctg ccttctcgat gtcccctctc tccactgcct agggccccct
 660
 45 acccaacccc aggacagcag cttccatcta tgagaagtgg cttcttagct tcctccagga
 720
 gctgtccttg tgggttgatg gagagtcccc aaggccccca gccctgggga tggggaagga
 780
 50 catgaagcct gagccagaga accagctata agtcctgaga agacactggt gtctggggac
 840
 agggagggat ggggtccctg atgaatatct ggagacctcg acagcctgcc ctaggccctg
 55 900

ggtgggtcag gacaaaggcc tctcatcacc gcagaaagcg ggggcttgca gggaaagtga
 960
 5 atgggcctgt ggccacctg gggtcacttg gaaaggatct gaataaaggg gacccttcct
 1020
 cg
 1022
 10
 <210> 67
 15 <211> 1190
 <212> DNA
 <213> Homo sapiens
 20
 <400> 67
 25 gtcagcagcc ccgacagccg acagtcacag cagctctgac aagagcgttc ctggagccca 60
 gtcctcttcc acagaccaca agcaccacgc agagaccatg ggccccccct cagccgctcc
 120
 30 ccgtggaggg cacaggccct ggagggggt cctgatcaca gcctcacttt taaccttctg
 180
 ggaccgccc accactgtcc agttcactat tgaagccctg ccatccagtg ctgcagaggg
 240
 35 aaaggatgtt cttctactgg cctgcaatat ttcagaaact attcaagcct attattggca
 300
 caaggggaaa acggcagaag ggagccctct cattgctggt tatataacag acattcaagc
 360
 40 aaatatccca ggggccgcat acagtggctg agagcaagta taccccaatg gatccctgct
 420
 45 gttccaaaac atcaccttgg aggacgcagg atcctacacc ctacgaacca taaatgccag
 480
 ttacgactct gaccaagcaa ctggccagct ccacgtacac caaaacaacg tcccaggcct
 540
 50 tcctgtgggg gccgtcgtg gcatcgtgac tggggtcctg gttggggtgg ctctggtggc
 600
 cgccctggtg tgttttctgc ttctctccag gactggaagg gccagcatcc agcgtgacct
 660
 55

cagggagcag ccgccccag cctccacccc tggccatggt ccctctcaca gatccacctt
720

5 ctcggcccct ctaccagcc ccagaacagc cactcccatc tatgtggaat ttctatactc
780

tgatgcaaac atttactgcc agatcgacca caaagcagat gtggtctctt aggttcctct
840

10 gggagctgct cttgtgggtt gatggagcgt cctcgaagct ccagccctgg ggacggggaa
900

ggacatggag cctgagccag agaaccagct ctgagtcctg aggagacaca ggcctgggga
960

15 cagggagggg tgggagtccc tgctgaatat ctggagaccc tgacagggtg ccctgggctc
1020

cggtggggcc gggacaaagg cctctcatca ccacaggaag cgggggcttg caaggaaagt
1080

gaatgggcct gtggcccacc cggggtcacc aggaaaggat ctgaataaag aggacccttc
1140

25 ctctcattgg ctctttttct gctcacggga acttagcaga aactcacctg
1190

30 <210> 68

<211> 2249

<212> DNA

35 <213> Homo sapiens

40 <400> 68

ctcctctaca aagaggtgga cagagaagac agcagagacc atgggacccc cctcagcccc 60

tccctgcaga ttgcatgtcc cctggaagga ggtcctgctc acagcctcac ttctaacctt
45 120

ctggaaccca cccaccactg ccaagctcac tattgaatcc acgccattca atgtcgcaga
180

50 ggggaaggag gttctttctac tcgcccacaa cctgccccag aatcgtattg gttacagctg
240

gtacaaaggc gaaagagtgg atggcaacag tctaattgta ggatatgtaa taggaactca
300

55

acaagctacc ccagggcccc catacagtgg tcgagagaca atatacccca atgcatccct
 360
 5 gctgatccag aacgtcacc agaatgacac aggattctat accctacaag tcataaagtc
 420
 agatcttggt aatgaagaag caaccggaca gttccatgta taccgggagc tgcccaagcc
 480
 10 ctccatctcc agcaacaact ccaaccccggt ggaggacaag gatgctgtgg ccttcacctg
 540
 tgaacctgag gttcagaaca caacctacct gtggtgggta aatggtcaga gcctcccggg
 600
 15 cagtcccagg ctgcagctgt ccaatggcaa catgaccctc actctactca gcgtcaaaag
 660
 gaacgatgca ggatcctatg aatgtgaaat acagaacca gcgagtgcc accgcagtga
 720
 20 cccagtcacc ctgaatgtcc tctatggccc agatgtcccc accatttccc cctcaaaggc
 780
 25 caattaccgt ccaggggaaa atctgaacct ctctgccac gcagcctcta acccacctgc
 840
 acagtactct tggtttatca atgggacgtt ccagcaatcc acacaagagc tctttatccc
 900
 30 caacatcact gtgaataata gcggatccta tatgtgcaa gcccataact cagccactgg
 960
 cctcaatagg accacagtca cgatgatcac agtctctgga agtgctcctg tcctctcagc
 1020
 35 tgtggccacc gtcggcatca cgattggagt gctggccagg gtggctctga tatagcagcc
 1080
 40 ctggtgtatt ttcgatattt caggaagact ggagattgg accagaccct gaattcttct
 1140
 agtcctcca atccatttt atcccatgga accactaaaa acaaggctctg ctctgctcct
 1200
 45 gaagccctat atgctggaga tggacaactc aatgaaaatt taaagggaaa accctcaggc
 1260
 ctgaggtgtg tgccactcag agacttcacc taactagaga cagtcaaact gcaaaccatg
 1320
 50 gtgagaaatt gacgacttca cactatggac agcttttccc aagatgtcaa aacaagactc
 1380
 55 ctcatcatga taaggctctt accccctttt aatttgcct tgcttatgcc tgctctttc
 1440

gcttggcagg atgatgctgt cattagtatt tcacaagaag tagcttcaga gggtaactta
1500

5 acagagtgtc agatctatct tgtcaatccc aacgttttac ataaaaataag agatccttta
1560

gtgcacccag tgactgacat tagcagcatc tttaacacag ccgtgtgttc aaatgtacag
1620

10 tggtcctttt cagagttgga cttctagact cacctgttct cactccctgt tttaattcaa
1680

cccagccatg caatgccaaa taatagaatt gctccctacc agctgaacag ggaggagtct
1740

15 gtgcagtttc tgacacttgt tgttgaacat ggctaaatac aatgggtatc gctgagacta
1800

20 agttgtagaa attaacaaat gtgctgcttg gttaaaatgg ctacactcat ctgactcatt
1860

ctttattcta ttttagttgg ttgtatctt gcctaagggt cgtagtccaa ctcttggtat
1920

25 taccctccta atagtcatac tagtagtcat actccctggt gtagtgtatt ctctaaaagc
1980

tttaaagtgc tgcatgcagc cagccatcaa atagtgaatg gtctctcttt ggctggaatt
2040

30 acaaaactca gagaaatgtg tcatcaggag aacatcataa cccatgaagg ataaaagccc
2100

35 caaatggtgg taactgataa tagcactaat gctttaagat ttggtcacac tctcacctag
2160

gtgagcgcat tgagccagtg gtgctaaatg ctacatactc caactgaaat gttaaggaag
2220

40 aagatagatc caaaaaaaaa aaaaaaaaaa
2249

45 <210> 69

<211> 2292

<212> DNA

50 <213> Homo sapiens

55 <400> 69

ccatgggttc cccttcagcc tgtccatata gagtgtgcat tccctggcag gggctcctgc 60
 5 tcacagcctc gcttttaacc ttctggaacc tgccaaacag tgcccagacc aatattgatg
 120
 tcgtgccgtt caatgtcgca gaagggaagg aggtccttct agtagtccat aatgagtccc
 180
 10 agaatcttta tggctacaac tggtaaaaag gggaaagggg gcatgccaac tatcgaatta
 240
 taggatattg aaaaaatata agtcaagaaa atgccccagg gcccgcacac aacggtcgag
 300
 15 agacaatata cccaatgga accctgctga tccagaacgt taccacaat gacgcaggat
 360
 tctataccct acacgttata aaagaaaatc ttgtgaatga agaagtaacc agacaattct
 420
 20 acgtattctc ggagccaccc aagccctcca tcaccagcaa caacttcaat ccggtggaga
 480
 acaaagatat tgtggtttta acctgtcaac ctgagactca gaacacaacc tacctgtggt
 540
 25 gggtaaacia tcagagcctc ctggtcagtc ccaggctgct gctctccact gacaacagga
 600
 30 cctcgttct actcagcgcc acaaagaatg acataggacc ctatgaatgt gaaatacaga
 660
 acccagtggg tgccagccgc agtgaccag tcaccctgaa tgtccgctat gagtcagtac
 720
 35 aagcaagttc acctgacctc tcagctggga ccgctgtcag catcatgatt ggagtactgg
 780
 ctgggatggc tctgatatag cagccttggg tagtttctg catttcggga agagtgtttt
 840
 tattatccac ctgcagactg gactggattc ttctagctcc ttcaatccca ttttctcctg
 900
 45 tggcatcact aagtataaga cctgctctct tctgaagac ctataagctg gaggtggaca
 960
 actcaatgta aatttcaagg aaaaaccctc atgcctgaga tgtggggcac tcagagctaa
 1020
 50 ccaaaatggt caacaccata actagagaca ctcaaattgc caaccaggac aagaagttga
 1080
 tgacttcatg ctgtggacag tttttcccaa gatgtccaa gcctcatcgt gacgaggctc
 1140
 55

ttatcccact ccatttttcc ctgctcatgc ctgcctcttt aatttggtta gataatgctg
 1200
 5 taactagaat ttcacaatca gcgccttggt caggcaattt gacagagtgt tggatgtgtc
 1260
 atgtcatcat gtcaaaccga aatatttgac ctaagggatc ctttattctg cccagtggct
 1320
 10 aactttaaca acatccctaa tacaactggt tattcaaag cagggtgggc cctgttagag
 1380
 ttagacctct agactcacct gttctcacgc cctgttttaa ttaaccag ctatgggatg
 1440
 15 ccagataaca gaattgctgc ctacgagctg aacagggagg agtttggtga gttgctgaca
 1500
 20 cttcttggtg cacataaata aatacagtg gtactataga gactcagttg caaaaattaa
 1560
 caaatatgct gcttgattaa aatgggtagg cttctcatgt ggctcattct ttaatctatt
 1620
 25 ctcttttatt tggtttggtt catgggggtc ctgcctatgg atcatacttc aaactcttg
 1680
 tgtgatcctc ctgattgtca caatattagt taccctgggt tgctgtattc tctaaaacct
 1740
 30 ttaaatgttt gcatgcagcc attcgtcaaa tgtcaaata tctctcttg gctggaatga
 1800
 caaaaactca aataaatgta tgattaggag gacatcataa cctatgaatg atggaagtcc
 1860
 35 aaaatgatgg taactgacag tagtgtaaat gccttatggt tagtcaaact ctcatttagg
 1920
 40 tgacagcctg gtgactccag aatggagcca gtcagtctaa atgccatata ctcacactga
 1980
 aacatgagga agcaggtaga tcccagaaca gacaaaactt tcctaaaaac atgagagtcc
 2040
 45 aggctgtctg agtcagcaca gtaagaaagt cctttctgct ttaactctta gaaaaaagta
 2100
 atatgaagta ttctgaaatt aaccaatcag tttatttaaa tcaatttatt tatattcttc
 2160
 50 tgttcttgga ttcccatctt acaaaaccca ctgttctact gttgtattgc ccagtaggag
 2220
 ctatcactat attttgcaga atggaaactg ccctgactct tgaatcaca ataaaagcca
 2280

attgtatctg tt
2292

5

<210> 70

<211> 2297

10

<212> DNA

<213> Homo sapiens

15

<400> 70

agccgtgctc agaaagtffc tggatcccag gctcatctcc acagaggaga acacgcaggc 60

20

agcagagacc atggggccca tctcagcccc ttctgcaga tggcgcatcc cctggcaggg
120

gctcctgctc acagcctcac ttttcacctt ctggaaccg cccaccactg ctgagctcac
180

25

tattgaagct gtgccatcca atgctgcaga ggggaaggag gttcttctac ttgtccacaa
240

tctgccccag gaccctcgtg gctacaactg gtacaaagg gaaacagtgg atgccaaccg
300

30

tcgaattata ggatatgtaa tatcaaatca acagattacc ccagggcctg catacagcaa
360

35

tcgagagaca atatacccca atgcatccct gctgatgcgg aacgtcacca gaaatgacac
420

aggatcctac accctacaag tcataaagct aaatcttatg agtgaagaag taactggcca
480

40

gttcagcgta catccggaga ctcccaagcc ctccatctcc agcaacaact ccaaccccg
540

ggaggacaag gatgctgtgg ccttcacctg tgaacctgag actcagaaca caacctac
600

45

gtggtgggta aatggtcaga gtctcccgt cagtcccagg ctgcagctgt ccaatggcaa
660

caggaccctc actctactca gtgtcacaag gaatgacgta ggaccctatg aatgtgaaat
720

50

acagaaccca gcgagtgcaa acttcagtga cccagtcacc ctgaatgtcc tctatggccc
780

55

agatgcccc accatttccc cttcagacac ctattacat gcaggggtaa atctcaacct
 840

5 ctcctgccat gcggcctcta atccaccctc acagtattct tggctgtgca atggcacatt
 900

ccagcaatac acacaaaagc tctttatccc caacatcact acaagaaca gcggatccta
 960

10 tgcctgccac accactaact cagccactgg ccgcaacagg accacagtca ggatgatcac
 1020

15 agtctctgat gctttagtag aaggaagttc tcttggcctc tcagctagag ccactgtcag
 1080

catcatgatt ggagtactgg ccagggtggc tctgatatag tagctctggt gtagtttctg
 1140

20 catttcaaga agactggcag acagttgttt ttattcttcc tcaaagcatt tgcaatcagc
 1200

taccattcaa aattgcttct tcttcaagat ttatggaaaa tactctgacg agtactcttg
 1260

25 aacacaagtt cctgataact ttaagatcac gccactggac tgtctatgaa cttgcaaaca
 1320

ggctgatacc tttgtgaagt tgcccaccaa aacacagaag gaaaaaaca tgaatttcat
 1380

30 tgaactaaat aataatgagg ataatgtttt taagattttt tttttttttt gagatggaat
 1440

35 ctgcctctgt cgcccaggct ggagtgcagt ggcacgatct caactcactg caagctccgc
 1500

ctctgggtt cacaccattc tcttgcctca gcctcctgag tagctgggac tacaggcgcc
 1560

40 tgccacaacg cccggctaatt tttttgtatt tttagtagag acgggggttc actgtggtct
 1620

caatctcctg acttcatggt ccgcctgcct cagcctcca aagttctggg attacaggtg
 1680

45 tgagccaccg cgcccagccc gtttttaaga ttttttattt gaaaaattgc caattcttta
 1740

agtgttttct ttttcagatt tatgaatttc tttatctttt aagctatcta taccttactg
 1800

caatttggtg aagcagactt ttgtgaacaa aaattataac atttactttt gctccctacc
 1860

55 tgactgccac agaactgggc aactattcat gagtattcat atgtttatgg taattcagtt
 1920

atttgacaaa gttcagtga aatctgctgt ctttataatg ggatatagtt taaaacattg
1980

5 gttatattac caaggctttg attgggatgt tatatttgag aaaatacaga gaatgataga
2040

ttaacggagt gtctaatac tctgtgtcaac cccaaatttt tacgtatgag atcctttagt
2100

10 ccacccaatg gctgacagta acagcatctt taacacaact ctttgttcaa atgtactatg
2160

gtctctttta gagtcagact cctagactca cttgttctca ctgtctgttt taatttaacc
2220

15 caggcatgca atgctagata ataaaattgc tccctattgg ctgatcaaaa aaaaaaaaaa
2280

20 aaaaaaaaaa aaaaaaa
2297

<210> 71

25 <211> 1552

<212> DNA

30 <213> Homo sapiens

<400> 71

35 gcccgtagac accgtgtgct gggacacccc acagtcagcc gcatggctcc cctgtgcccc 60

agccctggc tccctctgtt gatcccgcc cctgctccag gcctcactgt gcaactgctg
120

40 ctgtcactgc tgcttctgat gcctgtccat cccagaggt tgccccggat gcaggaggat
180

tccccttgg gaggaggctc ttctggggaa gatgaccac tgggcgagga ggatctgccc
240

45 agtgaagagg attcaccag agaggaggat ccaccggag aggaggatct acctggagag
300

50 gaggatctac ctggagagga ggatctacct gaagttaagc ctaaatcaga agaagagggc
360

tccctgaagt tagaggatct acctactgtt gaggtctctg gagatcctca agaaccacag
420

55

EP 1 439 393 A2

aataatgccc acagggacaa agaaggggat gaccagagtc attggcgcta tggaggcgac
480

5 ccgccctggc cccgggtgtc ccagcctgc gcgggcccgt tccagtcccc ggtggatata
540

cgccccagc tcgccgcctt ctgcccgcc ctgcgcccc tggaactcct gggcttccag
600

10 ctcccgccgc tcccagaact gcgcctgcgc aacaatggcc acagtgtgca actgaccctg
660

cctcctgggc tagagatggc tctgggtccc gggcgggagt accgggctct gcagctgcat
720

15 ctgcactggg gggctgcagg tcgtccgggc tcggagcaca ctgtggaagg ccaccgtttc
780

cctgccgaga tccacgtggt tcacctcagc accgcctttg ccagagtga cgaggccttg
840

gggcgcccgg gaggcctggc cgtgttgccc gcctttctgg aggaggggcc ggaagaaaac
900

25 agtgccatg agcagttgct gtctcgcttg gaagaaatcg ctgaggaagg ctacagagact
960

caggctccag gactggacat atctgcactc ctgccctctg acttcagccg ctacttccaa
1020

30 tatgaggggt ctctgactac accgccctgt gccagggtg tcactctggac tgtgtttaac
1080

cagacagtga tgctgagtgc taagcagctc cacaccctct ctgacaccct gtggggacct
1140

ggtgactctc ggctacagct gaacttccga gcgacgcagc ctttgaatgg gcgagtgatt
1200

40 gaggcctcct tccctgctgg agtggacagc agtcctcggg ctgctgagcc agtccagctg
1260

aattcctgcc tggctgctgg tgacatccta gccctggttt ttggcctcct ttttgctgtc
1320

45 accagcgtcg cgctccttgt gcagatgaga aggcagcaca gaagggaac caaaggggtg
1380

gtgagctacc gccagcaga ggtagccgag actggagcct agaggctgga tcttgagaa
1440

50 tgtgagaagc cagccagagg catctgaggg ggagccggtg actgtcctgt cctgctcatt
1500

atgccacttc cttttaactg ccaagaaatt ttttaaaata aatatttata at
1552

<210> 72
 5 <211> 702
 <212> PRT
 10 <213> Homo sapiens

<400> 72
 15 Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
 1 5 10 15
 20 Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
 20 25 30
 Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
 25 35 40 45
 Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
 50 55 60
 30 Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
 65 70 75 80
 35 Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser
 85 90 95
 Gly Arg Glu Ile Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Ile
 40 100 105 110
 Ile Gln Asn Asp Thr Gly Phe Tyr Thr Leu His Val Ile Lys Ser Asp
 45 115 120 125
 Leu Val Asn Glu Glu Ala Thr Gly Gln Phe Arg Val Tyr Pro Glu Leu
 130 135 140
 50 Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro Val Glu Asp Lys
 145 150 155 160
 55 Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Ala Thr Tyr
 165 170 175

EP 1 439 393 A2

Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
180 185 190

5 Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn Val Thr Arg Asn
195 200 205

10 Asp Thr Ala Ser Tyr Lys Cys Glu Thr Gln Asn Pro Val Ser Ala Arg
210 215 220

Arg Ser Asp Ser Val Ile Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro
15 225 230 235 240

Thr Ile Ser Pro Leu Asn Thr Ser Tyr Arg Ser Gly Glu Asn Leu Asn
20 245 250 255

Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe
260 265 270

25 Val Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn
275 280 285

Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys Gln Ala His Asn Ser
30 290 295 300

Asp Thr Gly Leu Asn Arg Thr Thr Val Thr Thr Ile Thr Val Tyr Ala
35 305 310 315 320

Glu Pro Pro Lys Pro Phe Ile Thr Ser Asn Asn Ser Asn Pro Val Glu
325 330 335

40 Asp Glu Asp Ala Val Ala Leu Thr Cys Glu Pro Glu Ile Gln Asn Thr
340 345 350

Thr Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg
45 355 360 365

Leu Gln Leu Ser Asn Asp Asn Arg Thr Leu Thr Leu Leu Ser Val Thr
50 370 375 380

Arg Asn Asp Val Gly Pro Tyr Glu Cys Gly Ile Gln Asn Glu Leu Ser
385 390 395 400

55 Val Asp His Ser Asp Pro Val Ile Leu Asn Val Leu Tyr Gly Pro Asp

EP 1 439 393 A2

	405	410	415
5	Asp Pro Thr Ile Ser Pro Ser Tyr Thr Tyr Tyr Arg Pro Gly Val Asn		
	420	425	430
	Leu Ser Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser		
10	435	440	445
	Trp Leu Ile Asp Gly Asn Ile Gln Gln His Thr Gln Glu Leu Phe Ile		
	450	455	460
15	Ser Asn Ile Thr Glu Lys Asn Ser Gly Leu Tyr Thr Cys Gln Ala Asn		
	465	470	475
20	Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val Lys Thr Ile Thr Val		
	485	490	495
	Ser Ala Glu Leu Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro		
25	500	505	510
	Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Ala Gln		
	515	520	525
30	Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser		
	530	535	540
35	Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn		
	545	550	555
	Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys Gly Ile Gln Asn Ser		
40	565	570	575
	Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu Asp Val Leu Tyr Gly		
45	580	585	590
	Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser Ser Tyr Leu Ser Gly		
	595	600	605
50	Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser Asn Pro Ser Pro Gln		
	610	615	620
55	Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln His Thr Gln Val Leu		
	625	630	635
			640

EP 1 439 393 A2

Phe Ile Ala Lys Ile Thr Pro Asn Asn Asn Gly Thr Tyr Ala Cys Phe
645 650 655
5 Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser Ile Val Lys Ser Ile
660 665 670
10 Thr Val Ser Ala Ser Gly Thr Ser Pro Gly Leu Ser Ala Gly Ala Thr
675 680 685
Val Gly Ile Met Ile Gly Val Leu Val Gly Val Ala Leu Ile
15 690 695 700
20
<210> 73
<211> 609
25 <212> PRT
<213> Homo sapiens
30
<400> 73
Met Lys Trp Val Glu Ser Ile Phe Leu Ile Phe Leu Leu Asn Phe Thr
35 1 5 10 15
Glu Ser Arg Thr Leu His Arg Asn Glu Tyr Gly Ile Ala Ser Ile Leu
20 25 30
40 Asp Ser Tyr Gln Cys Thr Ala Glu Ile Ser Leu Ala Asp Leu Ala Thr
35 40 45
45 Ile Phe Phe Ala Gln Phe Val Gln Glu Ala Thr Tyr Lys Glu Val Ser
50 55 60
Lys Met Val Lys Asp Ala Leu Thr Ala Ile Glu Lys Pro Thr Gly Asp
50 65 70 75 80
Glu Gln Ser Ser Gly Cys Leu Glu Asn Gln Leu Pro Ala Phe Leu Glu
85 90 95
55 Glu Leu Cys His Glu Lys Glu Ile Leu Glu Lys Tyr Gly His Ser Asp

EP 1 439 393 A2

	100	105	110
	Cys Cys Ser Gln Ser Glu Glu Gly Arg His Asn Cys Phe Leu Ala His		
5	115	120	125
	Lys Lys Pro Thr Pro Ala Ser Ile Pro Leu Phe Gln Val Pro Glu Pro		
10	130	135	140
	Val Thr Ser Cys Glu Ala Tyr Glu Glu Asp Arg Glu Thr Phe Met Asn		
	145	150	155
15	Lys Phe Ile Tyr Glu Ile Ala Arg Arg His Pro Phe Leu Tyr Ala Pro		
	165	170	175
20	Thr Ile Leu Leu Trp Ala Ala Arg Tyr Asp Lys Ile Ile Pro Ser Cys		
	180	185	190
	Cys Lys Ala Glu Asn Ala Val Glu Cys Phe Gln Thr Lys Ala Ala Thr		
25	195	200	205
	Val Thr Lys Glu Leu Arg Glu Ser Ser Leu Leu Asn Gln His Ala Cys		
	210	215	220
30	Ala Val Met Lys Asn Phe Gly Thr Arg Thr Phe Gln Ala Ile Thr Val		
	225	230	235
35	Thr Lys Leu Ser Gln Lys Phe Thr Lys Val Asn Phe Thr Glu Ile Gln		
	245	250	255
	Lys Leu Val Leu Asp Val Ala His Val His Glu His Cys Cys Arg Gly		
40	260	265	270
	Asp Val Leu Asp Cys Leu Gln Asp Gly Glu Lys Ile Met Ser Tyr Ile		
	275	280	285
45	Cys Ser Gln Gln Asp Thr Leu Ser Asn Lys Ile Thr Glu Cys Cys Lys		
	290	295	300
50	Leu Thr Thr Leu Glu Arg Gly Gln Cys Ile Ile His Ala Glu Asn Asp		
	305	310	315
	Glu Lys Pro Glu Gly Leu Ser Pro Asn Leu Asn Arg Phe Leu Gly Asp		
55	325	330	335

EP 1 439 393 A2

Arg Asp Phe Asn Gln Phe Ser Ser Gly Glu Lys Asn Ile Phe Leu Ala
340 345 350
5 Ser Phe Val His Glu Tyr Ser Arg Arg His Pro Gln Leu Ala Val Ser
355 360 365
10 Val Ile Leu Arg Val Ala Lys Gly Tyr Gln Glu Leu Leu Glu Lys Cys
370 375 380
Phe Gln Thr Glu Asn Pro Leu Glu Cys Gln Asp Lys Gly Glu Glu Glu
15 385 390 395 400
Leu Gln Lys Tyr Ile Gln Glu Ser Gln Ala Leu Ala Lys Arg Ser Cys
405 410 415
20 Gly Leu Phe Gln Lys Leu Gly Glu Tyr Tyr Leu Gln Asn Ala Phe Leu
420 425 430
25 Val Ala Tyr Thr Lys Lys Ala Pro Gln Leu Thr Ser Ser Glu Leu Met
435 440 445
Ala Ile Thr Arg Lys Met Ala Ala Thr Ala Ala Thr Cys Cys Gln Leu
30 450 455 460
Ser Glu Asp Lys Leu Leu Ala Cys Gly Glu Gly Ala Ala Asp Ile Ile
35 465 470 475 480
Ile Gly His Leu Cys Ile Arg His Glu Met Thr Pro Val Asn Pro Gly
485 490 495
40 Val Gly Gln Cys Cys Thr Ser Ser Tyr Ala Asn Arg Arg Pro Cys Phe
500 505 510
45 Ser Ser Leu Val Val Asp Glu Thr Tyr Val Pro Pro Ala Phe Ser Asp
515 520 525
Asp Lys Phe Ile Phe His Lys Asp Leu Cys Gln Ala Gln Gly Val Ala
50 530 535 540
Leu Gln Thr Met Lys Gln Glu Phe Leu Ile Asn Leu Val Lys Gln Lys
545 550 555 560
55 Pro Gln Ile Thr Glu Glu Gln Leu Glu Ala Val Ile Ala Asp Phe Ser

EP 1 439 393 A2

565 570 575
 Gly Leu Leu Glu Lys Cys Cys Gln Gly Gln Glu Gln Glu Val Cys Phe
 5 580 585 590
 Ala Glu Glu Gly Gln Lys Leu Ile Ser Lys Thr Arg Ala Ala Leu Gly
 10 595 600 605
 Val
 15
 20 <210> 74
 <211> 99
 <212> PRT
 25 <213> Homo sapiens
 30 <400> 74
 Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser
 1 5 10 15
 35 Ala Ala Leu Cys Glu Gly Ala Val Leu Pro Arg Ser Ala Lys Glu Leu
 20 25 30
 Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe
 40 35 40 45
 Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr
 45 50 55 60
 Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro
 65 70 75 80
 50 Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala
 85 90 95
 55 Glu Asn Ser

5 <210> 75
 <211> 300
 10 <212> PRT
 <213> Homo sapiens

 15 <400> 75
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1 5 10 15
 20 Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
 20 25 30
 25 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
 35 40 45
 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser
 30 50 55 60
 Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp
 35 65 70 75 80
 Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp
 85 90 95
 40 Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
 100 105 110
 Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
 45 115 120 125
 Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
 50 130 135 140
 Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
 145 150 155 160
 55 Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr

EP 1 439 393 A2

	165	170	175
5	Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro		
	180	185	190
	Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys		
10	195	200	205
	Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His		
	210	215	220
15	Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser		
	225	230	235
20	Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser		
	245	250	255
	Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val		
25	260	265	270
	Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile		
	275	280	285
30	Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn		
	290	295	300
35			
	<210> 76		
40	<211> 871		
	<212> PRT		
45	<213> Homo sapiens		
	<400> 76		
50	Met Lys Tyr Ser Cys Cys Ala Leu Val Leu Ala Val Leu Gly Thr Glu		
	1	5	10
	15		
55	Leu Leu Gly Ser Leu Cys Ser Thr Val Arg Ser Pro Arg Phe Arg Gly		
	20	25	30

EP 1 439 393 A2

Arg Ile Gln Gln Glu Arg Lys Asn Ile Arg Pro Asn Ile Ile Leu Val
35 40 45

5 Leu Thr Asp Asp Gln Asp Val Glu Leu Gly Ser Leu Gln Val Met Asn
50 55 60

10 Lys Thr Arg Lys Ile Met Glu His Gly Gly Ala Thr Phe Ile Asn Ala
65 70 75 80

Phe Val Thr Thr Pro Met Cys Cys Pro Ser Arg Ser Ser Met Leu Thr
15 85 90 95

Gly Lys Tyr Val His Asn His Asn Val Tyr Thr Asn Asn Glu Asn Cys
100 105 110

20 Ser Ser Pro Ser Trp Gln Ala Met His Glu Pro Arg Thr Phe Ala Val
115 120 125

25 Tyr Leu Asn Asn Thr Gly Tyr Arg Thr Ala Phe Phe Gly Lys Tyr Leu
130 135 140

Asn Glu Tyr Asn Gly Ser Tyr Ile Pro Pro Gly Trp Arg Glu Trp Leu
30 145 150 155 160

Gly Leu Ile Lys Asn Ser Arg Phe Tyr Asn Tyr Thr Val Cys Arg Asn
35 165 170 175

Gly Ile Lys Glu Lys His Gly Phe Asp Tyr Ala Lys Asp Tyr Phe Thr
180 185 190

40 Asp Leu Ile Thr Asn Glu Ser Ile Asn Tyr Phe Lys Met Ser Lys Arg
195 200 205

Met Tyr Pro His Arg Pro Val Met Met Val Ile Ser His Ala Ala Pro
45 210 215 220

His Gly Pro Glu Asp Ser Ala Pro Gln Phe Ser Lys Leu Tyr Pro Asn
50 225 230 235 240

Ala Ser Gln His Ile Thr Pro Ser Tyr Asn Tyr Ala Pro Asn Met Asp
245 250 255

55 Lys His Trp Ile Met Gln Tyr Thr Gly Pro Met Leu Pro Ile His Met

EP 1 439 393 A2

	260	265	270
	Glu Phe Thr Asn Ile Leu Gln Arg Lys Arg Leu Gln Thr Leu Met Ser		
5	275	280	285
	Val Asp Asp Ser Val Glu Arg Leu Tyr Asn Met Leu Val Glu Thr Gly		
10	290	295	300
	Glu Leu Glu Asn Thr Tyr Ile Ile Tyr Thr Ala Asp His Gly Tyr His		
	305	310	315
15	Ile Gly Gln Phe Gly Leu Val Lys Gly Lys Ser Met Pro Tyr Asp Phe		
	325	330	335
20	Asp Ile Arg Val Pro Phe Phe Ile Arg Gly Pro Ser Val Glu Pro Gly		
	340	345	350
	Ser Ile Val Pro Gln Ile Val Leu Asn Ile Asp Leu Ala Pro Thr Ile		
25	355	360	365
	Leu Asp Ile Ala Gly Leu Asp Thr Pro Pro Asp Val Asp Gly Lys Ser		
	370	375	380
30	Val Leu Lys Leu Leu Asp Pro Glu Lys Pro Gly Asn Arg Phe Arg Thr		
	385	390	395
35	Asn Lys Lys Ala Lys Ile Trp Arg Asp Thr Phe Leu Val Glu Arg Gly		
	405	410	415
	Lys Phe Leu Arg Lys Lys Glu Glu Ser Ser Lys Asn Ile Gln Gln Ser		
40	420	425	430
	Asn His Leu Pro Lys Tyr Glu Arg Val Lys Glu Leu Cys Gln Gln Ala		
45	435	440	445
	Arg Tyr Gln Thr Ala Cys Glu Gln Pro Gly Gln Lys Trp Gln Cys Ile		
	450	455	460
50	Glu Asp Thr Ser Gly Lys Leu Arg Ile His Lys Cys Lys Gly Pro Ser		
	465	470	475
	Asp Leu Leu Thr Val Arg Gln Ser Thr Arg Asn Leu Tyr Ala Arg Gly		
55	485	490	495

EP 1 439 393 A2

	Phe His Asp Lys Asp Lys Glu Cys Ser Cys Arg Glu Ser Gly Tyr Arg	
	500	505 510
5	Ala Ser Arg Ser Gln Arg Lys Ser Gln Arg Gln Phe Leu Arg Asn Gln	
	515	520 525
10	Gly Thr Pro Lys Tyr Lys Pro Arg Phe Val His Thr Arg Gln Thr Arg	
	530	535 540
	Ser Leu Ser Val Glu Phe Glu Gly Glu Ile Tyr Asp Ile Asn Leu Glu	
15	545	550 555 560
	Glu Glu Glu Glu Leu Gln Val Leu Gln Pro Arg Asn Ile Ala Lys Arg	
	565	570 575
20	His Asp Glu Gly His Lys Gly Pro Arg Asp Leu Gln Ala Ser Ser Gly	
	580	585 590
25	Gly Asn Arg Gly Arg Met Leu Ala Asp Ser Ser Asn Ala Val Gly Pro	
	595	600 605
	Pro Thr Thr Val Arg Val Thr His Lys Cys Phe Ile Leu Pro Asn Asp	
30	610	615 620
	Ser Ile His Cys Glu Arg Glu Leu Tyr Gln Ser Ala Arg Ala Trp Lys	
35	625	630 635 640
	Asp His Lys Ala Tyr Ile Asp Lys Glu Ile Glu Ala Leu Gln Asp Lys	
	645	650 655
40	Ile Lys Asn Leu Arg Glu Val Arg Gly His Leu Lys Arg Arg Lys Pro	
	660	665 670
45	Glu Glu Cys Ser Cys Ser Lys Gln Ser Tyr Tyr Asn Lys Glu Lys Gly	
	675	680 685
	Val Lys Lys Gln Glu Lys Leu Lys Ser His Leu His Pro Phe Lys Glu	
50	690	695 700
	Ala Ala Gln Glu Val Asp Ser Lys Leu Gln Leu Phe Lys Glu Asn Asn	
	705	710 715 720
55	Arg Arg Arg Lys Lys Glu Arg Lys Glu Lys Arg Arg Gln Arg Lys Gly	

EP 1 439 393 A2

	725	730	735
	Glu Glu Cys Ser Leu Pro Gly Leu Thr Cys Phe Thr His Asp Asn Asn		
5	740	745	750
	His Trp Gln Thr Ala Pro Phe Trp Asn Leu Gly Ser Phe Cys Ala Cys		
10	755	760	765
	Thr Ser Ser Asn Asn Asn Thr Tyr Trp Cys Leu Arg Thr Val Asn Glu		
	770	775	780
15	Thr His Asn Phe Leu Phe Cys Glu Phe Ala Thr Gly Phe Leu Glu Tyr		
	785	790	795 800
20	Phe Asp Met Asn Thr Asp Pro Tyr Gln Leu Thr Asn Thr Val His Thr		
	805	810	815
	Val Glu Arg Gly Ile Leu Asn Gln Leu His Val Gln Leu Met Glu Leu		
25	820	825	830
	Arg Ser Cys Gln Gly Tyr Lys Gln Cys Asn Pro Arg Pro Lys Asn Leu		
	835	840	845
30	Asp Val Gly Asn Lys Asp Gly Gly Ser Tyr Asp Leu His Arg Gly Gln		
	850	855	860
35	Leu Trp Asp Gly Trp Glu Gly		
	865	870	
40			
	<210> 77		
45	<211> 470		
	<212> PRT		
	<213> Homo sapiens		
50			
	<400> 77		
55	Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala		
	1	5	10 15

EP 1 439 393 A2

Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe
 20 25 30
 5 Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu
 35 40 45
 10 Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile
 50 55 60
 Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp
 15 65 70 75 80
 Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp
 85 90 95
 20 Leu His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His
 100 105 110
 25 Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu
 115 120 125
 Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val
 30 130 135 140
 Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu
 35 145 150 155 160
 Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly
 165 170 175
 40 Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly
 180 185 190
 Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly
 45 195 200 205
 Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu
 50 210 215 220
 Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr
 225 230 235 240
 55 Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg

EP 1 439 393 A2

	245	250	255
5	Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro		
	260	265	270
	Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe		
10	275	280	285
	Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg		
	290	295	300
15	Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu		
	305	310	315
	Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr		
20	325	330	335
	Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr		
25	340	345	350
	Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile		
	355	360	365
30	His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val		
	370	375	380
35	Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr		
	385	390	395
	Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys		
40	405	410	415
	Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val		
45	420	425	430
	Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln		
	435	440	445
50	Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser		
	450	455	460
	Asn Ser Trp Phe Gly Cys		
55	465	470	

5 <210> 78
 <211> 165
 <212> PRT
 10 <213> Homo sapiens

15 <400> 78
 Met Ala Pro Asn Ala Ser Cys Leu Cys Val His Val Arg Ser Glu Glu
 1 5 10 15
 20 Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys
 20 25 30
 25 Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln
 35 40 45
 Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser
 30 50 55 60
 Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val
 65 70 75 80
 35 Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly
 85 90 95
 40 Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val
 100 105 110
 Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu
 45 115 120 125
 Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met
 50 130 135 140
 Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser
 145 150 155 160
 55 Tyr Cys Ile Gly Gly

165

5

<210> 79

10

<211> 1464

<212> PRT

<213> Homo sapiens

15

<400> 79

20

Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Leu Ala Ala Thr

1 5 10 15

Ala Leu Leu Thr His Gly Gln Glu Glu Gly Gln Val Glu Gly Gln Asp

25

20 25 30

Glu Asp Ile Pro Pro Ile Thr Cys Val Gln Asn Gly Leu Arg Tyr His

35 40 45

30

Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg Ile Cys Val Cys Asp

50 55 60

35

Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys Asp Glu Thr Lys Asn

65 70 75 80

Cys Pro Gly Ala Glu Val Pro Glu Gly Glu Cys Cys Pro Val Cys Pro

40

85 90 95

Asp Gly Ser Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly

100 105 110

45

Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala Gly Pro

115 120 125

50

Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Pro Gly Pro Pro

130 135 140

Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala

55

145 150 155 160

EP 1 439 393 A2

Pro Gln Leu Ser Tyr Gly Tyr Asp Glu Lys Ser Thr Gly Gly Ile Ser
165 170 175

5 Val Pro Gly Pro Met Gly Pro Ser Gly Pro Arg Gly Leu Pro Gly Pro
180 185 190

10 Pro Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro
195 200 205

Gly Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro Pro Gly
15 210 215 220

Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly Arg
225 230 235 240

20 Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg Gly Leu Pro
245 250 255

25 Gly Thr Ala Gly Leu Pro Gly Met Lys Gly His Arg Gly Phe Ser Gly
260 265 270

Leu Asp Gly Ala Lys Gly Asp Ala Gly Pro Ala Gly Pro Lys Gly Glu
30 275 280 285

Pro Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg
35 290 295 300

Gly Leu Pro Gly Glu Arg Gly Arg Pro Gly Ala Pro Gly Pro Ala Gly
305 310 315 320

40 Ala Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro Gly Pro
325 330 335

Thr Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly Ala Lys
45 340 345 350

Gly Glu Ala Gly Pro Gln Gly Pro Arg Gly Ser Glu Gly Pro Gln Gly
50 355 360 365

Val Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Ala Ala Gly Pro
370 375 380

55 Ala Gly Asn Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Ala Asn

EP 1 439 393 A2

	385	390	395	400
	Gly Ala Pro Gly Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala Arg Gly			
5		405	410	415
	Pro Ser Gly Pro Gln Gly Pro Gly Gly Pro Pro Gly Pro Lys Gly Asn			
10		420	425	430
	Ser Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly Ala Lys			
	435	440	445	
15	Gly Glu Pro Gly Pro Val Gly Val Gln Gly Pro Pro Gly Pro Ala Gly			
	450	455	460	
20	Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Thr Gly Leu			
	465	470	475	480
	Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly Phe Pro			
25		485	490	495
	Gly Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly			
	500	505	510	
30	Ser Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg			
	515	520	525	
35	Pro Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro			
	530	535	540	
	Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly			
40	545	550	555	560
	Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly Gln			
	565	570	575	
45	Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly Glu Pro			
	580	585	590	
50	Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly			
	595	600	605	
	Pro Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro			
55	610	615	620	

EP 1 439 393 A2

Ala Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro
625 630 635 640

5 Gly Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly
645 650 655

10 Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro
660 665 670

15 Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val Gln
675 680 685

Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala Pro Gly
690 695 700

20 Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser
705 710 715 720

25 Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala
725 730 735

Gly Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly
740 745 750

30 Ala Asp Gly Ser Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro
755 760 765

35 Ile Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ser
770 775 780

40 Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly
785 790 795 800

45 Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro
805 810 815

Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Glu Pro Gly Asp Ala
820 825 830

50 Gly Ala Lys Gly Asp Ala Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly
835 840 845

55 Pro Pro Gly Pro Ile Gly Asn Val Gly Ala Pro Gly Ala Lys Gly Ala

EP 1 439 393 A2

	850	855	860	
	Arg Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala			
5	865	870	875	880
	Gly Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly			
	885	890	895	
10	Pro Pro Gly Pro Ala Gly Lys Glu Gly Gly Lys Gly Pro Arg Gly Glu			
	900	905	910	
15	Thr Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro			
	915	920	925	
	Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala Gly			
20	930	935	940	
	Ala Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly Val			
25	945	950	955	960
	Val Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro			
	965	970	975	
30	Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly			
	980	985	990	
35	Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro			
	995	1000	1005	
	Pro Gly Glu Ser Gly Arg Glu Gly Ala Pro Ala Ala Glu Gly Ser Pro			
40	1010	1015	1020	
	Gly Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly Glu Thr Gly			
45	1025	1030	1035	1040
	Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala Pro Gly Pro			
	1045	1050	1055	
50	Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala			
	1060	1065	1070	
	Gly Pro Ala Gly Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala Gly			
55	1075	1080	1085	

EP 1 439 393 A2

Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp
1090 1095 1100

5 Arg Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro
1105 1110 1115 1120

10 Gly Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser Gly
1125 1130 1135

Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ala Pro Gly Lys
15 1140 1145 1150

Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg
1155 1160 1165

20 Gly Arg Thr Gly Asp Ala Gly Pro Val Gly Pro Pro Gly Pro Pro Gly
1170 1175 1180

25 Pro Pro Gly Pro Pro Gly Pro Pro Ser Ala Gly Phe Asp Phe Ser Phe
1185 1190 1195 1200

Leu Pro Gln Pro Pro Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr
30 1205 1210 1215

Arg Ala Asp Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp
1220 1225 1230

35 Thr Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser Pro
1235 1240 1245

40 Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys Met
1250 1255 1260

Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn Gln
45 1265 1270 1275 1280

Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly
50 1285 1290 1295

Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Ala Gln Lys Asn Trp
1300 1305 1310

55 Tyr Ile Ser Lys Asn Pro Lys Asp Lys Arg His Val Trp Phe Gly Glu

EP 1 439 393 A2

	1315	1320	1325
	Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp		
5	1330	1335	1340
	Pro Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser Thr		
10	1345	1350	1355
	Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr		1360
	1365	1370	1375
15	Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Leu Lys Gly		
	1380	1385	1390
20	Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr		
	1395	1400	1405
	Ser Val Thr Val Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys		
25	1410	1415	1420
	Thr Val Ile Glu Tyr Lys Thr Thr Lys Ser Ser Arg Leu Pro Ile Ile		
	1425	1430	1435
30	Asp Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe		1440
	1445	1450	1455
35	Asp Val Gly Pro Val Cys Phe Leu		
	1460		
40			
	<210> 80		
45	<211> 338		
	<212> PRT		
	<213> Homo sapiens		
50			
	<400> 80		
55	Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr		
	1	5	10
			15

EP 1 439 393 A2

Ser Gly Gln Tyr Tyr Asp Tyr Asp Phe Pro Leu Ser Ile Tyr Gly Gln
20 25 30

5 Ser Ser Pro Asn Cys Ala Pro Glu Cys Asn Cys Pro Glu Ser Tyr Pro
35 40 45

10 Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val
50 55 60

Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His
15 65 70 75 80

Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile
85 90 95

20 Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe
100 105 110

25 Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu
115 120 125

Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu
30 130 135 140

Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn
35 145 150 155 160

Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val
165 170 175

40 Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
180 185 190

Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
45 195 200 205

Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr
50 210 215 220

Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
225 230 235 240

55 Leu Ala Asp Ser Gly Ile Pro Gly Asn Ser Phe Asn Val Ser Ser Leu

EP 1 439 393 A2

245 250 255
 Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
 5 260 265 270
 Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys
 10 275 280 285
 Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser
 290 295 300
 15 Lys Ile Lys His Leu Arg Leu Asp Gly Asn Arg Ile Ser Glu Thr Ser
 305 310 315 320
 Leu Pro Pro Asp Met Tyr Glu Cys Leu Arg Val Ala Asn Glu Val Thr
 20 325 330 335
 Leu Asn
 25
 30 <210> 81
 <211> 589
 35 <212> PRT
 <213> Homo sapiens
 40 <400> 81
 Met Ser Val Ser Val His Glu Asn Arg Lys Ser Arg Ala Ser Ser Gly
 45 1 5 10 15
 Ser Ile Asn Ile Tyr Leu Phe His Lys Ser Ser Tyr Ala Asp Ser Val
 20 25 30
 50 Leu Thr His Leu Asn Leu Leu Arg Gln Gln Arg Leu Phe Thr Asp Val
 35 40 45
 Leu Leu His Ala Gly Asn Arg Thr Phe Pro Cys His Arg Ala Val Leu
 55 50 55 60

EP 1 439 393 A2

Ala Ala Cys Ser Arg Tyr Phe Glu Ala Met Phe Ser Gly Gly Leu Lys
65 70 75 80
5 Glu Ser Gln Asp Ser Glu Val Asn Phe Asp Asn Ser Ile His Pro Glu
85 90 95
10 Val Leu Glu Leu Leu Leu Asp Tyr Ala Tyr Ser Ser Arg Val Ile Ile
100 105 110
Asn Glu Glu Asn Ala Glu Ser Leu Leu Glu Ala Gly Asp Met Leu Glu
15 115 120 125
Phe Gln Asp Ile Arg Asp Ala Cys Ala Glu Phe Leu Glu Lys Asn Leu
130 135 140
20 His Pro Thr Asn Cys Leu Gly Met Leu Leu Leu Ser Asp Ala His Gln
145 150 155 160
25 Cys Thr Lys Leu Tyr Glu Leu Ser Trp Arg Met Cys Leu Ser Asn Phe
165 170 175
Gln Thr Ile Arg Lys Asn Glu Asp Phe Leu Gln Leu Pro Gln Asp Met
30 180 185 190
Val Val Gln Leu Leu Ser Ser Glu Glu Leu Glu Thr Glu Asp Glu Arg
35 195 200 205
Leu Val Tyr Glu Ser Ala Ile Asn Trp Ile Ser Tyr Asp Leu Lys Lys
210 215 220
40 Arg Tyr Cys Tyr Leu Pro Glu Leu Leu Gln Thr Val Arg Leu Ala Leu
225 230 235 240
Leu Pro Ala Ile Tyr Leu Met Glu Asn Val Ala Met Glu Glu Leu Ile
45 245 250 255
Thr Lys Gln Arg Lys Ser Lys Glu Ile Val Glu Glu Ala Ile Arg Cys
50 260 265 270
Lys Leu Lys Ile Leu Gln Asn Asp Gly Val Val Thr Ser Leu Cys Ala
275 280 285
55 Arg Pro Arg Lys Thr Gly His Ala Leu Phe Leu Leu Gly Gly Gln Thr

EP 1 439 393 A2

	290	295	300	
	Phe Met Cys Asp Lys Leu Tyr Leu Val Asp Gln Lys Ala Lys Glu Ile			
5	305	310	315	320
	Ile Pro Lys Ala Asp Ile Pro Ser Pro Arg Lys Glu Phe Ser Ala Cys			
10	325	330	335	
	Ala Ile Gly Cys Lys Val Tyr Ile Thr Gly Gly Arg Gly Ser Glu Asn			
	340	345	350	
15	Gly Val Ser Lys Asp Val Trp Val Tyr Asp Thr Leu His Glu Glu Trp			
	355	360	365	
20	Ser Lys Ala Ala Pro Met Leu Val Ala Arg Phe Gly His Gly Ser Ala			
	370	375	380	
	Glu Leu Lys His Cys Leu Tyr Val Val Gly Gly His Thr Ala Ala Thr			
25	385	390	395	400
	Gly Cys Leu Pro Ala Ser Pro Ser Val Ser Leu Lys Gln Val Glu His			
	405	410	415	
30	Tyr Asp Pro Thr Ile Asn Lys Trp Thr Met Val Ala Pro Leu Arg Glu			
	420	425	430	
35	Gly Val Ser Asn Ala Ala Val Val Ser Ala Lys Leu Lys Leu Phe Ala			
	435	440	445	
	Phe Gly Gly Thr Ser Val Ser His Asp Lys Leu Pro Lys Val Gln Cys			
40	450	455	460	
	Tyr Asp Gln Cys Glu Asn Arg Trp Thr Val Pro Ala Thr Cys Pro Gln			
45	465	470	475	480
	Pro Trp Arg Tyr Thr Ala Ala Ala Val Leu Gly Asn Gln Ile Phe Ile			
	485	490	495	
50	Met Gly Gly Asp Thr Glu Phe Ser Ala Cys Ser Ala Tyr Lys Phe Asn			
	500	505	510	
	Ser Glu Thr Tyr Gln Trp Thr Lys Val Gly Asp Val Thr Ala Lys Arg			
55	515	520	525	

EP 1 439 393 A2

Met Ser Cys His Ala Val Ala Ser Gly Asn Lys Leu Tyr Val Val Gly
530 535 540

5 Gly Tyr Phe Gly Ile Gln Arg Cys Lys Thr Leu Asp Cys Tyr Asp Pro
545 550 555 560

10 Thr Leu Asp Val Trp Asn Ser Ile Thr Thr Val Pro Tyr Ser Leu Ile
565 570 575

Pro Thr Ala Phe Val Ser Thr Trp Lys His Leu Pro Ser
15 580 585

20 <210> 82
<211> 193
25 <212> PRT
<213> Homo sapiens

30 <400> 82

Met Ile Arg Cys Gly Leu Ala Cys Glu Arg Cys Arg Trp Ile Leu Pro
1 5 10 15

35 Leu Leu Leu Leu Ser Ala Ile Ala Phe Asp Ile Ile Ala Leu Ala Gly
20 25 30

40 Arg Gly Trp Leu Gln Ser Ser Asp His Gly Gln Thr Ser Ser Leu Trp
35 40 45

45 Trp Lys Cys Ser Gln Glu Gly Gly Gly Ser Gly Ser Tyr Glu Glu Gly
50 55 60

Cys Gln Ser Leu Met Glu Tyr Ala Trp Gly Arg Ala Ala Ala Ala Met
50 65 70 75 80

Leu Phe Cys Gly Phe Ile Ile Leu Val Ile Cys Phe Ile Leu Ser Phe
85 90 95

55 Phe Ala Leu Cys Gly Pro Gln Met Leu Val Phe Leu Arg Val Ile Gly

EP 1 439 393 A2

100 105 110
 Gly Leu Leu Ala Leu Ala Ala Val Phe Gln Ile Ile Ser Leu Val Ile
 5 115 120 125
 Tyr Pro Val Lys Tyr Thr Gln Thr Phe Thr Leu His Ala Asn Pro Ala
 10 130 135 140
 Val Thr Tyr Ile Tyr Asn Trp Ala Tyr Gly Phe Gly Trp Ala Ala Thr
 145 150 155 160
 15 Ile Ile Leu Ile Gly Cys Ala Phe Phe Phe Cys Cys Leu Leu Asn Tyr
 165 170 175
 Glu Asp Asp Leu Leu Gly Asn Ala Lys Pro Arg Tyr Phe Tyr Thr Ser
 20 180 185 190
 Ala
 25
 30 <210> 83
 <211> 423
 <212> PRT
 35 <213> Homo sapiens
 40 <400> 83
 Met Arg Ser Ser Gly Ala Asp Ala Gly Arg Cys Leu Val Thr Ala Arg
 1 5 10 15
 45 Ala Pro Gly Ser Val Pro Ala Ser Arg Glu Gly Ser Ala Gly Ser Arg
 20 25 30
 50 Gly Pro Gly Ala Arg Phe Pro Ala Arg Val Ser Ala Arg Gly Ser Ala
 35 40 45
 Pro Gly Pro Gly Leu Gly Gly Ala Gly Ala Leu Asp Pro Pro Ala Val
 55 50 55 60

EP 1 439 393 A2

Val Ala Glu Ser Val Ser Ser Leu Thr Ile Ala Asp Ala Phe Ile Ala
65 70 75 80
5 Ala Gly Glu Ser Ser Ala Pro Thr Pro Pro Arg Pro Ala Leu Pro Arg
85 90 95
10 Arg Phe Ile Cys Ser Phe Pro Asp Cys Ser Ala Asn Tyr Ser Lys Ala
100 105 110
Trp Lys Leu Asp Ala His Leu Cys Lys His Thr Gly Glu Arg Pro Phe
15 115 120 125
Val Cys Asp Tyr Glu Gly Cys Gly Lys Ala Phe Ile Arg Asp Tyr His
130 135 140
20 Leu Ser Arg His Ile Leu Thr His Thr Gly Glu Lys Pro Phe Val Cys
145 150 155 160
25 Ala Ala Asn Gly Cys Asp Gln Lys Phe Asn Thr Lys Ser Asn Leu Lys
165 170 175
Lys His Phe Glu Arg Lys His Glu Asn Gln Gln Lys Gln Tyr Ile Cys
30 180 185 190
Ser Phe Glu Asp Cys Lys Lys Thr Phe Lys Lys His Gln Gln Leu Lys
195 200 205
35 Ile His Gln Cys Gln Asn Thr Asn Glu Pro Leu Phe Lys Cys Thr Gln
210 215 220
40 Glu Gly Cys Gly Lys His Phe Ala Ser Pro Ser Lys Leu Lys Arg His
225 230 235 240
Ala Lys Ala His Glu Gly Tyr Val Cys Gln Lys Gly Cys Ser Phe Val
45 245 250 255
Ala Lys Thr Trp Thr Glu Leu Leu Lys His Val Arg Glu Thr His Lys
50 260 265 270
Glu Glu Ile Leu Cys Glu Val Cys Arg Lys Thr Phe Lys Arg Lys Asp
275 280 285
55 Tyr Leu Lys Gln His Met Lys Thr His Ala Pro Glu Arg Asp Val Cys

EP 1 439 393 A2

290 295 300
 Arg Cys Pro Arg Glu Gly Cys Gly Arg Thr Tyr Thr Thr Val Phe Asn
 5 305 310 315 320
 Leu Gln Ser His Ile Leu Ser Phe His Glu Glu Ser Arg Pro Phe Val
 10 325 330 335
 Cys Glu His Ala Gly Cys Gly Lys Thr Phe Ala Met Lys Gln Ser Leu
 340 345 350
 15 Thr Arg His Ala Val Val His Asp Pro Asp Lys Lys Lys Met Lys Leu
 355 360 365
 Lys Val Lys Lys Ser Arg Glu Lys Arg Glu Phe Gly Leu Ser Ser Gln
 20 370 375 380
 Trp Ile Tyr Pro Pro Lys Arg Lys Gln Gly Gln Gly Leu Ser Leu Cys
 25 385 390 395 400
 Gln Asn Gly Glu Ser Pro Asn Cys Val Glu Asp Lys Met Leu Ser Thr
 405 410 415
 30 Val Ala Val Leu Thr Leu Gly
 420
 35
 <210> 84
 40 <211> 339
 <212> PRT
 45 <213> Homo sapiens
 <400> 84
 50 Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn
 1 5 10 15
 55 Ala Arg Ser Arg Pro Ser Phe His Pro Leu Ser Asp Glu Leu Val Asn
 20 25 30

EP 1 439 393 A2

Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr
 35 40 45
 5 Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly
 50 55 60
 Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu
 10 65 70 75 80
 Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile
 15 85 90 95
 Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly
 100 105 110
 20 Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His
 115 120 125
 Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser
 25 130 135 140
 Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn
 30 145 150 155 160
 Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His
 165 170 175
 35 Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn
 180 185 190
 Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser
 40 195 200 205
 Lys Ile Cys Glu Pro Gly Tyr Ser Pro Thr Tyr Lys Gln Asp Lys His
 45 210 215 220
 Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met
 50 225 230 235 240
 Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr
 245 250 255
 55 Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly

EP 1 439 393 A2

260 265 270
 5 Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val Glu
 275 280 285
 Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp Trp
 10 290 295 300
 Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys Gly
 305 310 315 320
 15 Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr Trp
 325 330 335
 20 Glu Lys Ile
 25
 <210> 85
 <211> 150
 30 <212> PRT
 <213> Homo sapiens
 35
 <400> 85
 Met Ala Ala Arg Gly Val Ile Ala Pro Val Gly Glu Ser Leu Arg Tyr
 40 1 5 10 15
 Ala Glu Tyr Leu Gln Pro Ser Ala Lys Arg Pro Asp Ala Asp Val Asp
 45 20 25 30
 Gln Gln Gly Leu Val Arg Ser Leu Ile Ala Val Gly Leu Gly Val Ala
 35 40 45
 50 Ala Leu Ala Phe Ala Gly Arg Tyr Ala Phe Arg Ile Trp Lys Pro Leu
 50 55 60
 Glu Gln Val Ile Thr Glu Thr Ala Lys Lys Ile Ser Thr Pro Ser Phe
 55 65 70 75 80

EP 1 439 393 A2

Ser Ser Tyr Tyr Lys Gly Gly Phe Glu Gln Lys Met Ser Arg Arg Glu
 5 85 90 95
 Ala Gly Leu Ile Leu Gly Val Ser Pro Ser Ala Gly Lys Ala Lys Ile
 100 105 110
 10 Arg Thr Ala His Arg Arg Val Met Ile Leu Asn His Pro Asp Lys Gly
 115 120 125
 15 Gly Ser Pro Tyr Val Ala Ala Lys Ile Asn Glu Ala Lys Asp Leu Leu
 130 135 140
 Glu Thr Thr Thr Lys His
 20 145 150

 25 <210> 86
 <211> 1212
 30 <212> PRT
 <213> Homo sapiens

 35 <400> 86
 Met Glu Pro Arg Pro Thr Ala Pro Ser Ser Gly Ala Pro Gly Leu Ala
 1 5 10 15
 40 Gly Val Gly Glu Thr Pro Ser Ala Ala Ala Leu Ala Ala Ala Arg Val
 20 25 30
 45 Glu Leu Pro Gly Thr Ala Val Pro Ser Val Pro Glu Asp Ala Ala Pro
 35 40 45
 Ala Ser Arg Asp Gly Gly Gly Val Arg Asp Glu Gly Pro Ala Ala Ala
 50 50 55 60
 Gly Asp Gly Leu Gly Arg Pro Leu Gly Pro Thr Pro Ser Gln Ser Arg
 55 65 70 75 80
 Phe Gln Val Asp Leu Val Ser Glu Asn Ala Gly Arg Ala Ala Ala Ala

EP 1 439 393 A2

	85	90	95
5	Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Gly Ala Gly Ala Gly		
	100	105	110
	Ala Lys Gln Thr Pro Ala Asp Gly Glu Ala Ser Gly Glu Ser Glu Pro		
10	115	120	125
	Ala Lys Gly Ser Glu Glu Ala Lys Gly Arg Phe Arg Val Asn Phe Val		
15	130	135	140
	Asp Pro Ala Ala Ser Ser Ser Ala Glu Asp Ser Leu Ser Asp Ala Ala		
	145	150	155
20	Gly Val Gly Val Asp Gly Pro Asn Val Ser Phe Gln Asn Gly Gly Asp		
	165	170	175
	Thr Val Leu Ser Glu Gly Ser Ser Leu His Ser Gly Gly Gly Gly Gly		
25	180	185	190
	Ser Gly His His Gln His Tyr Tyr Tyr Asp Thr His Thr Asn Thr Tyr		
30	195	200	205
	Tyr Leu Arg Thr Phe Gly His Asn Thr Met Asp Ala Val Pro Arg Ile		
	210	215	220
35	Asp His Tyr Arg His Thr Ala Ala Gln Leu Gly Glu Lys Leu Leu Arg		
	225	230	235
	Pro Ser Leu Ala Glu Leu His Asp Glu Leu Glu Lys Glu Pro Phe Glu		
40	245	250	255
	Asp Gly Phe Ala Asn Gly Glu Glu Ser Thr Pro Thr Arg Asp Ala Val		
45	260	265	270
	Val Thr Tyr Thr Ala Glu Ser Lys Gly Val Val Lys Phe Gly Trp Ile		
	275	280	285
50	Lys Gly Val Leu Val Arg Cys Met Leu Asn Ile Trp Gly Val Met Leu		
	290	295	300
	Phe Ile Arg Leu Ser Trp Ile Val Gly Gln Ala Gly Ile Gly Leu Ser		
55	305	310	315
			320

EP 1 439 393 A2

Val Leu Val Ile Met Met Ala Thr Val Val Thr Thr Ile Thr Gly Leu
5 325 330 335
Ser Thr Ser Ala Ile Ala Thr Asn Gly Phe Val Arg Gly Gly Gly Ala
340 345 350
10 Tyr Tyr Leu Ile Ser Arg Ser Leu Gly Pro Glu Phe Gly Gly Ala Ile
355 360 365
Gly Leu Ile Phe Ala Phe Ala Asn Ala Val Ala Val Ala Met Tyr Val
15 370 375 380
Val Gly Phe Ala Glu Thr Val Val Glu Leu Leu Lys Glu His Ser Ile
20 385 390 395 400
Leu Met Ile Asp Glu Ile Asn Asp Ile Arg Ile Ile Gly Ala Ile Thr
405 410 415
25 Val Val Ile Leu Leu Gly Ile Ser Val Ala Gly Met Glu Trp Glu Ala
420 425 430
Lys Ala Gln Ile Val Leu Leu Val Ile Leu Leu Leu Ala Ile Gly Asp
30 435 440 445
Phe Val Ile Gly Thr Phe Ile Pro Leu Glu Ser Lys Lys Pro Lys Gly
35 450 455 460
Phe Phe Gly Tyr Lys Ser Glu Ile Phe Asn Glu Asn Phe Gly Pro Asp
465 470 475 480
40 Phe Arg Glu Glu Glu Thr Phe Phe Ser Val Phe Ala Ile Phe Phe Pro
485 490 495
45 Ala Ala Thr Gly Ile Leu Ala Gly Ala Asn Ile Ser Gly Asp Leu Ala
500 505 510
Asp Pro Gln Ser Ala Ile Pro Lys Gly Thr Leu Leu Ala Ile Leu Ile
50 515 520 525
Thr Thr Leu Val Tyr Val Gly Ile Ala Val Ser Val Gly Ser Cys Val
530 535 540
55 Val Arg Asp Ala Thr Gly Asn Val Asn Asp Thr Ile Val Thr Glu Leu

EP 1 439 393 A2

	545	550	555	560
5	Thr Asn Cys Thr Ser Ala Ala Cys Lys Leu Asn Phe Asp Phe Ser Ser			
		565	570	575
	Cys Glu Ser Ser Pro Cys Ser Tyr Gly Leu Met Asn Asn Phe Gln Val			
10		580	585	590
	Met Ser Met Val Ser Gly Phe Thr Pro Leu Ile Ser Ala Gly Ile Phe			
		595	600	605
15	Ser Ala Thr Leu Ser Ser Ala Leu Ala Ser Leu Val Ser Ala Pro Lys			
		610	615	620
20	Ile Phe Gln Ala Leu Cys Lys Asp Asn Ile Tyr Pro Ala Phe Gln Met			
		625	630	635
	Phe Ala Lys Gly Tyr Gly Lys Asn Asn Glu Pro Leu Arg Gly Tyr Ile			
25		645	650	655
	Leu Thr Phe Leu Ile Ala Leu Gly Phe Ile Leu Ile Ala Glu Leu Asn			
		660	665	670
30	Val Ile Ala Pro Ile Ile Ser Asn Phe Phe Leu Ala Ser Tyr Ala Leu			
		675	680	685
35	Ile Asn Phe Ser Val Phe His Ala Ser Leu Ala Lys Ser Pro Gly Trp			
		690	695	700
	Arg Pro Ala Phe Lys Tyr Tyr Asn Met Trp Ile Ser Leu Leu Gly Ala			
40		705	710	715
	Ile Leu Cys Cys Ile Val Met Phe Val Ile Asn Trp Trp Ala Ala Leu			
		725	730	735
45	Leu Thr Tyr Val Ile Val Leu Gly Leu Tyr Ile Tyr Val Thr Tyr Lys			
		740	745	750
50	Lys Pro Asp Val Asn Trp Gly Ser Ser Thr Gln Ala Leu Thr Tyr Leu			
		755	760	765
	Asn Ala Leu Gln His Ser Ile Arg Leu Ser Gly Val Glu Asp His Val			
55		770	775	780

EP 1 439 393 A2

Lys Asn Phe Arg Pro Gln Cys Leu Val Met Thr Gly Ala Pro Asn Ser
 5 785 790 795 800
 Arg Pro Ala Leu Leu His Leu Val His Asp Phe Thr Lys Asn Val Gly
 805 810 815
 10 Leu Met Ile Cys Gly His Val His Met Gly Pro Arg Arg Gln Ala Met
 820 825 830
 Lys Glu Met Ser Ile Asp Gln Ala Lys Tyr Gln Arg Trp Leu Ile Lys
 15 835 840 845
 Asn Lys Met Lys Ala Phe Tyr Ala Pro Val His Ala Asp Asp Leu Arg
 20 850 855 860
 Glu Gly Ala Gln Tyr Leu Met Gln Ala Ala Gly Leu Gly Arg Met Lys
 865 870 875 880
 25 Pro Asn Thr Leu Val Leu Gly Phe Lys Lys Asp Trp Leu Gln Ala Asp
 885 890 895
 Met Arg Asp Val Asp Met Tyr Ile Asn Leu Phe His Asp Ala Phe Asp
 30 900 905 910
 Ile Gln Tyr Gly Val Val Val Ile Arg Leu Lys Glu Gly Leu Asp Ile
 35 915 920 925
 Ser His Leu Gln Gly Gln Glu Glu Leu Leu Ser Ser Gln Glu Lys Ser
 930 935 940
 40 Pro Gly Thr Lys Asp Val Val Val Ser Val Glu Tyr Ser Lys Lys Ser
 945 950 955 960
 45 Asp Leu Asp Thr Ser Lys Pro Leu Ser Glu Lys Pro Ile Thr His Lys
 965 970 975
 Val Glu Glu Glu Asp Gly Lys Thr Ala Thr Gln Pro Leu Leu Lys Lys
 50 980 985 990
 Glu Ser Lys Gly Pro Ile Val Pro Leu Asn Val Ala Asp Gln Lys Leu
 995 1000 1005
 55 Leu Glu Ala Ser Thr Gln Phe Gln Lys Lys Gln Gly Lys Asn Thr Ile

EP 1 439 393 A2

	1010	1015	1020	
5	Asp Val Trp Trp Leu Phe Asp Asp Gly Gly Leu Thr Leu Leu Ile Pro			
	1025	1030	1035	1040
	Tyr Leu Leu Thr Thr Lys Lys Lys Trp Lys Asp Cys Lys Ile Arg Val			
10		1045	1050	1055
	Phe Ile Gly Gly Lys Ile Asn Arg Ile Asp His Asp Arg Arg Ala Met			
	1060	1065	1070	
15	Ala Thr Leu Leu Ser Lys Phe Arg Ile Asp Phe Ser Asp Ile Met Val			
	1075	1080	1085	
20	Leu Gly Asp Ile Asn Thr Lys Pro Lys Lys Glu Asn Ile Ile Ala Phe			
	1090	1095	1100	
	Glu Glu Ile Ile Glu Pro Tyr Arg Leu His Glu Asp Asp Lys Glu Gln			
25	1105	1110	1115	1120
	Asp Ile Ala Asp Lys Met Lys Glu Asp Glu Pro Trp Arg Ile Thr Asp			
	1125	1130	1135	
30	Asn Glu Leu Glu Leu Tyr Lys Thr Lys Thr Tyr Arg Gln Ile Arg Leu			
	1140	1145	1150	
35	Asn Glu Leu Leu Lys Glu His Ser Ser Thr Ala Asn Ile Ile Val Met			
	1155	1160	1165	
	Ser Leu Pro Val Ala Arg Lys Gly Ala Val Ser Ser Ala Leu Tyr Met			
40	1170	1175	1180	
	Ala Trp Leu Glu Ala Leu Ser Lys Asp Leu Pro Pro Ile Leu Leu Val			
45	1185	1190	1195	1200
	Arg Gly Asn His Gln Ser Val Leu Thr Phe Tyr Ser			
	1205	1210		
50				
55	<210> 87			
	<211> 230			

EP 1 439 393 A2

<212> PRT

<213> Homo sapiens

<400> 87

10 Met Asn Glu Met Tyr Leu Arg Cys Asp His Glu Asn Gln Tyr Ala Gln
1 5 10 15
15 Trp Met Ala Ala Cys Met Leu Ala Ser Lys Gly Lys Thr Met Ala Asp
20 25 30
Ser Ser Tyr Gln Pro Glu Val Leu Asn Ile Leu Ser Phe Leu Arg Met
20 35 40 45
Lys Asn Arg Asn Ser Ala Ser Gln Val Ala Ser Ser Leu Glu Asn Met
50 55 60
25 Asp Met Asn Pro Glu Cys Phe Val Ser Pro Arg Cys Ala Lys Arg His
65 70 75 80
30 Lys Ser Lys Gln Leu Ala Ala Arg Ile Leu Glu Ala His Gln Asn Val
85 90 95
Ala Gln Met Pro Leu Val Glu Ala Lys Leu Arg Phe Ile Gln Ala Trp
35 100 105 110
Gln Ser Leu Pro Glu Phe Gly Leu Thr Tyr Tyr Leu Val Arg Phe Lys
115 120 125
40 Gly Ser Lys Lys Asp Asp Ile Leu Gly Val Ser Tyr Asn Arg Leu Ile
130 135 140
45 Lys Ile Asp Ala Ala Thr Gly Ile Pro Val Thr Thr Trp Arg Phe Thr
145 150 155 160
Asn Ile Lys Gln Trp Asn Val Asn Trp Glu Thr Arg Gln Val Val Ile
50 165 170 175
Glu Phe Asp Gln Asn Val Phe Thr Ala Phe Thr Cys Leu Ser Ala Asp
180 185 190
55 Cys Lys Ile Val His Glu Tyr Ile Gly Gly Tyr Ile Phe Leu Ser Thr

EP 1 439 393 A2

	195	200	205
5	Arg Ser Lys Asp Gln Asn Glu Thr Leu Asp Glu Asp Leu Phe His Lys		
	210	215	220
	Leu Thr Gly Gly Gln Asp		
10	225	230	
15	<210> 88		
	<211> 383		
20	<212> PRT		
	<213> Homo sapiens		
25	<400> 88		
	Met Glu Ala Leu Gly Lys Leu Lys Gln Phe Asp Ala Tyr Pro Lys Thr		
30	1 5 10 15		
	Leu Glu Asp Phe Arg Val Lys Thr Cys Gly Gly Ala Thr Val Thr Ile		
	20 25 30		
35	Val Ser Gly Leu Leu Met Leu Leu Leu Phe Leu Ser Glu Leu Gln Tyr		
	35 40 45		
	Tyr Leu Thr Thr Glu Val His Pro Glu Leu Tyr Val Asp Lys Ser Arg		
40	50 55 60		
	Gly Asp Lys Leu Lys Ile Asn Ile Asp Val Leu Phe Pro His Met Pro		
45	65 70 75 80		
	Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp Val Ala Gly Glu Gln Gln		
	85 90 95		
50	Leu Asp Val Glu His Asn Leu Phe Lys Gln Arg Leu Asp Lys Asp Gly		
	100 105 110		
	Ile Pro Val Ser Ser Glu Ala Glu Arg His Glu Leu Gly Lys Val Glu		
55	115 120 125		

EP 1 439 393 A2

Val Thr Val Phe Asp Pro Asp Ser Leu Asp Pro Asp Arg Cys Glu Ser
5 130 135 140
Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys Cys Cys Asn Thr Cys Glu
145 150 155 160
10 Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly Trp Ala Phe Lys Asn Pro
165 170 175
15 Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly Phe Ser Gln Lys Met Gln
180 185 190
Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr Gly Phe Leu Glu Val Asn
20 195 200 205
Lys Val Ala Gly Asn Phe His Phe Ala Pro Gly Lys Ser Phe Gln Gln
210 215 220
25 Ser His Val His Val His Asp Leu Gln Ser Phe Gly Leu Asp Asn Ile
225 230 235 240
30 Asn Met Thr His Tyr Ile Gln His Leu Ser Phe Gly Glu Asp Tyr Pro
245 250 255
Gly Ile Val Asn Pro Leu Asp His Thr Asn Val Thr Ala Pro Gln Ala
35 260 265 270
Ser Met Met Phe Gln Tyr Phe Val Lys Val Val Pro Thr Val Tyr Met
275 280 285
40 Lys Val Asp Gly Glu Val Leu Arg Thr Asn Gln Phe Ser Val Thr Arg
290 295 300
45 His Glu Lys Val Ala Asn Gly Leu Leu Gly Asp Gln Gly Leu Pro Gly
305 310 315 320
Val Phe Val Leu Tyr Glu Leu Ser Pro Met Met Val Lys Leu Thr Glu
50 325 330 335
Lys His Arg Ser Phe Thr His Phe Leu Thr Gly Val Cys Ala Ile Ile
340 345 350
55 Gly Gly Met Phe Thr Val Ala Gly Leu Ile Asp Ser Leu Ile Tyr His

EP 1 439 393 A2

355 360 365
 5 Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp Leu Gly Lys Thr Thr
 370 375 380
 10
 <210> 89
 <211> 391
 15 <212> PRT
 <213> Homo sapiens
 20
 <400> 89
 Met Ala Asp Ile Asp Asn Lys Glu Gln Ser Glu Leu Asp Gln Asp Leu
 25 1 5 10 15
 Asp Asp Val Glu Glu Val Glu Glu Glu Glu Thr Gly Glu Glu Thr Lys
 30 20 25 30
 Leu Lys Ala Arg Gln Leu Thr Val Gln Met Met Gln Asn Pro Gln Ile
 35 35 40 45
 Leu Ala Ala Leu Gln Glu Arg Leu Asp Gly Leu Val Glu Thr Pro Thr
 50 55 60
 Gly Tyr Ile Glu Ser Leu Pro Arg Val Val Lys Arg Arg Val Asn Ala
 40 65 70 75 80
 Leu Lys Asn Leu Gln Val Lys Cys Ala Gln Ile Glu Ala Lys Phe Tyr
 45 85 90 95
 Glu Glu Val His Asp Leu Glu Arg Lys Tyr Ala Val Leu Tyr Gln Pro
 100 105 110
 50 Leu Phe Asp Lys Arg Phe Glu Ile Ile Asn Ala Ile Tyr Glu Pro Thr
 115 120 125
 55 Glu Glu Glu Cys Glu Trp Lys Pro Asp Glu Glu Asp Glu Ile Ser Glu
 130 135 140

EP 1 439 393 A2

Glu Leu Lys Glu Lys Ala Lys Ile Glu Asp Glu Lys Lys Asp Glu Glu
 5 145 150 155 160
 Lys Glu Asp Pro Lys Gly Ile Pro Glu Phe Trp Leu Thr Val Phe Lys
 165 170 175
 10 Asn Val Asp Leu Leu Ser Asp Met Val Gln Glu His Asp Glu Pro Ile
 180 185 190
 Leu Lys His Leu Lys Asp Ile Lys Val Lys Phe Ser Asp Ala Gly Gln
 15 195 200 205
 Pro Met Ser Phe Val Leu Glu Phe His Phe Glu Pro Asn Glu Tyr Phe
 20 210 215 220
 Thr Asn Glu Val Leu Thr Lys Thr Tyr Arg Met Arg Ser Glu Pro Asp
 225 230 235 240
 25 Asp Ser Asp Pro Phe Ser Phe Asp Gly Pro Glu Ile Met Gly Cys Thr
 245 250 255
 Gly Cys Gln Ile Asp Trp Lys Lys Gly Lys Asn Val Thr Leu Lys Thr
 30 260 265 270
 Ile Lys Lys Lys Gln Lys His Lys Gly Arg Gly Thr Val Arg Thr Val
 35 275 280 285
 Thr Lys Thr Val Ser Asn Asp Ser Phe Phe Asn Phe Phe Ala Pro Pro
 290 295 300
 40 Glu Val Pro Glu Ser Gly Asp Leu Asp Asp Asp Ala Glu Ala Ile Leu
 305 310 315 320
 45 Ala Ala Asp Phe Glu Ile Gly His Phe Leu Arg Glu Arg Ile Ile Pro
 325 330 335
 Arg Ser Val Leu Tyr Phe Thr Gly Glu Ala Ile Glu Asp Asp Asp Asp
 50 340 345 350
 Asp Tyr Asp Glu Glu Gly Glu Glu Ala Asp Glu Glu Gly Glu Glu Glu
 355 360 365
 55 Gly Asp Glu Glu Asn Asp Pro Asp Tyr Asp Pro Lys Lys Asp Gln Asn

EP 1 439 393 A2

370 375 380

5 Pro Ala Glu Cys Lys Gln Gln

385 390

10

<210> 90

<211> 836

15 <212> PRT

<213> Homo sapiens

20

<400> 90

Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Ile Val

25 1 5 10 15

Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser

30 20 25 30

Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln

35 35 40 45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr

50 55 60

Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys

40 65 70 75 80

Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu

45 85 90 95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr

100 105 110

50 Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly

115 120 125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn

55 130 135 140

EP 1 439 393 A2

Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
 5 145 150 155 160
 Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
 165 170 175
 10 Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu
 180 185 190
 Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys
 15 195 200 205
 Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His
 20 210 215 220
 Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe
 225 230 235 240
 25 Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr
 245 250 255
 Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe
 30 260 265 270
 Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu
 35 275 280 285
 Arg Phe Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His
 290 295 300
 40 Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val
 305 310 315 320
 45 Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp
 325 330 335
 Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys Asp Ile Val
 50 340 345 350
 Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu Ile Pro Asp
 355 360 365
 55 Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe

EP 1 439 393 A2

	370	375	380	
5	Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp			
	385	390	395	400
	Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp			
10		405	410	415
	Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His			
		420	425	430
15	Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile			
		435	440	445
20	Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr			
		450	455	460
	Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly			
25		465	470	475
	Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu			
		485	490	495
30	Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe			
		500	505	510
35	Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro			
		515	520	525
	Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met			
40		530	535	540
	Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln			
45		545	550	555
	Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly			
		565	570	575
50	Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys			
		580	585	590
	Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys			
55		595	600	605

EP 1 439 393 A2

Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val
5 610 615 620
Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu
625 630 635 640
10 Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val
 645 650 655
15 Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys
 660 665 670
Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser
20 675 680 685
Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys
 690 695 700
25 Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly Glu Thr Ile
705 710 715 720
30 Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys Ile
 725 730 735
Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu
35 740 745 750
Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly
 755 760 765
40 Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val
770 775 780
45 Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu
785 790 795 800
Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp Thr Pro Val Arg Lys
50 805 810 815
Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu
55 820 825 830
Gly Arg Ser Gln

835

5

<210> 91

10

<211> 3176

<212> PRT

15

<213> Homo sapiens

<400> 91

20

Met Arg Lys His Arg His Leu Pro Leu Val Ala Val Phe Cys Leu Phe

1

5

10

15

Leu Ser Gly Phe Pro Thr Thr His Ala Gln Gln Gln Gln Ala Asp Val

25

20

25

30

Lys Asn Gly Ala Ala Ala Asp Ile Ile Phe Leu Val Asp Ser Ser Trp

30

35

40

45

Thr Ile Gly Glu Glu His Phe Gln Leu Val Arg Glu Phe Leu Tyr Asp

50

55

60

35

Val Val Lys Ser Leu Ala Val Gly Glu Asn Asp Phe His Phe Ala Leu

65

70

75

80

Val Gln Phe Asn Gly Asn Pro His Thr Glu Phe Leu Leu Asn Thr Tyr

40

85

90

95

Arg Thr Lys Gln Glu Val Leu Ser His Ile Ser Asn Met Ser Tyr Ile

45

100

105

110

Gly Gly Thr Asn Gln Thr Gly Lys Gly Leu Glu Tyr Ile Met Gln Ser

115

120

125

50

His Leu Thr Lys Ala Ala Gly Ser Arg Ala Gly Asp Gly Val Pro Gln

130

135

140

Val Ile Val Val Leu Thr Asp Gly His Ser Lys Asp Gly Leu Ala Leu

55

145

150

155

160

Pro Ser Ala Glu Leu Lys Ser Ala Asp Val Asn Val Phe Ala Ile Gly
 5 165 170 175
 Val Glu Asp Ala Asp Glu Gly Ala Leu Lys Glu Ile Ala Ser Glu Pro
 180 185 190
 10 Leu Asn Met His Met Phe Asn Leu Glu Asn Phe Thr Ser Leu His Asp
 195 200 205
 Ile Val Gly Asn Leu Val Ser Cys Val His Ser Ser Val Ser Pro Glu
 15 210 215 220
 Arg Ala Gly Asp Thr Glu Thr Leu Lys Asp Ile Thr Ala Gln Asp Ser
 20 225 230 235 240
 Ala Asp Ile Ile Phe Leu Ile Asp Gly Ser Asn Asn Thr Gly Ser Val
 245 250 255
 25 Asn Phe Ala Val Ile Leu Asp Phe Leu Val Asn Leu Leu Glu Lys Leu
 260 265 270
 Pro Ile Gly Thr Gln Gln Ile Arg Val Gly Val Val Gln Phe Ser Asp
 30 275 280 285
 Glu Pro Arg Thr Met Phe Ser Leu Asp Thr Tyr Ser Thr Lys Ala Gln
 35 290 295 300
 Val Leu Gly Ala Val Lys Ala Leu Gly Phe Ala Gly Gly Glu Leu Ala
 305 310 315 320
 40 Asn Ile Gly Leu Ala Leu Asp Phe Val Val Glu Asn His Phe Thr Arg
 325 330 335
 45 Ala Gly Gly Ser Arg Val Glu Glu Gly Val Pro Gln Val Leu Val Leu
 340 345 350
 Ile Ser Ala Gly Pro Ser Ser Asp Glu Ile Arg Tyr Gly Val Val Ala
 50 355 360 365
 Leu Lys Gln Ala Ser Val Phe Ser Phe Gly Leu Gly Ala Gln Ala Ala
 370 375 380
 55 Ser Arg Ala Glu Leu Gln His Ile Ala Thr Asp Asp Asn Leu Val Phe

EP 1 439 393 A2

	385				390					395					400	
5	Thr	Val	Pro	Glu	Phe	Arg	Ser	Phe	Gly	Asp	Leu	Gln	Glu	Lys	Leu	Leu
					405					410					415	
	Pro	Tyr	Ile	Val	Gly	Val	Ala	Gln	Arg	His	Ile	Val	Leu	Lys	Pro	Pro
10				420					425					430		
	Thr	Ile	Val	Thr	Gln	Val	Ile	Glu	Val	Asn	Lys	Arg	Asp	Ile	Val	Phe
				435					440					445		
15																
	Leu	Val	Asp	Gly	Ser	Ser	Ala	Leu	Gly	Leu	Ala	Asn	Phe	Asn	Ala	Ile
				450					455					460		
20																
	Arg	Asp	Phe	Ile	Ala	Lys	Val	Ile	Gln	Arg	Leu	Glu	Ile	Gly	Gln	Asp
				465					470					475		480
	Leu	Ile	Gln	Val	Ala	Val	Ala	Gln	Tyr	Ala	Asp	Thr	Val	Arg	Pro	Glu
25																
				485						490					495	
	Phe	Tyr	Phe	Asn	Thr	His	Pro	Thr	Lys	Arg	Glu	Val	Ile	Thr	Ala	Val
30																
				500						505					510	
	Arg	Lys	Met	Lys	Pro	Leu	Asp	Gly	Ser	Ala	Leu	Tyr	Thr	Gly	Ser	Ala
				515						520					525	
35																
	Leu	Asp	Phe	Val	Arg	Asn	Asn	Leu	Phe	Thr	Ser	Ser	Ala	Gly	Tyr	Arg
				530						535					540	
	Ala	Ala	Glu	Gly	Ile	Pro	Lys	Leu	Leu	Val	Leu	Ile	Thr	Gly	Gly	Lys
40																
				545						550				555		560
	Ser	Leu	Asp	Glu	Ile	Ser	Gln	Pro	Ala	Gln	Glu	Leu	Lys	Arg	Ser	Ser
45																
				565							570					575
	Ile	Met	Ala	Phe	Ala	Ile	Gly	Asn	Lys	Gly	Ala	Asp	Gln	Ala	Glu	Leu
				580						585					590	
50																
	Glu	Glu	Ile	Ala	Phe	Asp	Ser	Ser	Leu	Val	Phe	Ile	Pro	Ala	Glu	Phe
				595						600					605	
55																
	Arg	Ala	Ala	Pro	Leu	Gln	Gly	Met	Leu	Pro	Gly	Leu	Leu	Ala	Pro	Leu
				610						615					620	

EP 1 439 393 A2

Arg Thr Leu Ser Gly Thr Pro Glu Val His Ser Asn Lys Arg Asp Ile
5 625 630 635 640
Ile Phe Leu Leu Asp Gly Ser Ala Asn Val Gly Lys Thr Asn Phe Pro
645 650 655
10 Tyr Val Arg Asp Phe Val Met Asn Leu Val Asn Ser Leu Asp Ile Gly
660 665 670
Asn Asp Asn Ile Arg Val Gly Leu Val Gln Phe Ser Asp Thr Pro Val
15 675 680 685
Thr Glu Phe Ser Leu Asn Thr Tyr Gln Thr Lys Ser Asp Ile Leu Gly
20 690 695 700
His Leu Arg Gln Leu Gln Leu Gln Gly Gly Ser Gly Leu Asn Thr Gly
705 710 715 720
25 Ser Ala Leu Ser Tyr Val Tyr Ala Asn His Phe Thr Glu Ala Gly Gly
725 730 735
Ser Arg Ile Arg Glu His Val Pro Gln Leu Leu Leu Leu Leu Thr Ala
30 740 745 750
Gly Gln Ser Glu Asp Ser Tyr Leu Gln Ala Ala Asn Ala Leu Thr Arg
35 755 760 765
Ala Gly Ile Leu Thr Phe Cys Val Gly Ala Ser Gln Ala Asn Lys Ala
770 775 780
40 Glu Leu Glu Gln Ile Ala Phe Asn Pro Ser Leu Val Tyr Leu Met Asp
785 790 795 800
45 Asp Phe Ser Ser Leu Pro Ala Leu Pro Gln Gln Leu Ile Gln Pro Leu
805 810 815
Thr Thr Tyr Val Ser Gly Gly Val Glu Glu Val Pro Leu Ala Gln Pro
50 820 825 830
Glu Ser Lys Arg Asp Ile Leu Phe Leu Phe Asp Gly Ser Ala Asn Leu
835 840 845
55 Val Gly Gln Phe Pro Val Val Arg Asp Phe Leu Tyr Lys Ile Ile Asp

EP 1 439 393 A2

	850	855	860
5	Glu Leu Asn Val Lys Pro Glu Gly Thr Arg Ile Ala Val Ala Gln Tyr		
	865	870	875 880
	Ser Asp Asp Val Lys Val Glu Ser Arg Phe Asp Glu His Gln Ser Lys		
10	885	890	895
	Pro Glu Ile Leu Asn Leu Val Lys Arg Met Lys Ile Lys Thr Gly Lys		
	900	905	910
15	Ala Leu Asn Leu Gly Tyr Ala Leu Asp Tyr Ala Gln Arg Tyr Ile Phe		
	915	920	925
20	Val Lys Ser Ala Gly Ser Arg Ile Glu Asp Gly Val Leu Gln Phe Leu		
	930	935	940
	Val Leu Leu Val Ala Gly Arg Ser Ser Asp Arg Val Asp Gly Pro Ala		
25	945	950	955 960
	Ser Asn Leu Lys Gln Ser Gly Val Val Pro Phe Ile Phe Gln Ala Lys		
	965	970	975
30	Asn Ala Asp Pro Ala Glu Leu Glu Gln Ile Val Leu Ser Pro Ala Phe		
	980	985	990
35	Ile Leu Ala Ala Glu Ser Leu Pro Lys Ile Gly Asp Leu His Pro Gln		
	995	1000	1005
	Ile Val Asn Leu Leu Lys Ser Val His Asn Gly Ala Pro Ala Pro Val		
40	1010	1015	1020
	Ser Gly Glu Lys Asp Val Val Phe Leu Leu Asp Gly Ser Glu Gly Val		
	1025	1030	1035 1040
45	Arg Ser Gly Phe Pro Leu Leu Lys Glu Phe Val Gln Arg Val Val Glu		
	1045	1050	1055
50	Ser Leu Asp Val Gly Gln Asp Arg Val Arg Val Ala Val Val Gln Tyr		
	1060	1065	1070
	Ser Asp Arg Thr Arg Pro Glu Phe Tyr Leu Asn Ser Tyr Met Asn Lys		
55	1075	1080	1085

EP 1 439 393 A2

Gln Asp Val Val Asn Ala Val Arg Gln Leu Thr Leu Leu Gly Gly Pro
1090 1095 1100
5 Thr Pro Asn Thr Gly Ala Ala Leu Glu Phe Val Leu Arg Asn Ile Leu
1105 1110 1115 1120
10 Val Ser Ser Ala Gly Ser Arg Ile Thr Glu Gly Val Pro Gln Leu Leu
1125 1130 1135
Ile Val Leu Thr Ala Asp Arg Ser Gly Asp Asp Val Arg Asn Pro Ser
15 1140 1145 1150
Val Val Val Lys Arg Gly Gly Ala Val Pro Ile Gly Ile Gly Ile Gly
1155 1160 1165
20 Asn Ala Asp Ile Thr Glu Met Gln Thr Ile Ser Phe Ile Pro Asp Phe
1170 1175 1180
25 Ala Val Ala Ile Pro Thr Phe Arg Gln Leu Gly Thr Val Gln Gln Val
1185 1190 1195 1200
Ile Ser Glu Arg Val Thr Gln Leu Thr Arg Glu Glu Leu Ser Arg Leu
30 1205 1210 1215
Gln Pro Val Leu Gln Pro Leu Pro Ser Pro Gly Val Gly Gly Lys Arg
35 1220 1225 1230
Asp Val Val Phe Leu Ile Asp Gly Ser Gln Ser Ala Gly Pro Glu Phe
1235 1240 1245
40 Gln Tyr Val Arg Thr Leu Ile Glu Arg Leu Val Asp Tyr Leu Asp Val
1250 1255 1260
45 Gly Phe Asp Thr Thr Arg Val Ala Val Ile Gln Phe Ser Asp Asp Pro
1265 1270 1275 1280
Lys Ala Glu Phe Leu Leu Asn Ala His Ser Ser Lys Asp Glu Val Gln
50 1285 1290 1295
Asn Ala Val Gln Arg Leu Arg Pro Lys Gly Gly Arg Gln Ile Asn Val
1300 1305 1310
55 Gly Asn Ala Leu Glu Tyr Val Ser Arg Asn Ile Phe Lys Arg Pro Leu

EP 1 439 393 A2

	1315	1320	1325	
	Gly Ser Arg Ile Glu Glu Gly Val Pro Gln Phe Leu Val Leu Ile Ser			
5	1330	1335	1340	
	Ser Gly Lys Ser Asp Asp Glu Val Val Val Pro Ala Val Glu Leu Lys			
10	1345	1350	1355	1360
	Gln Phe Gly Val Ala Pro Phe Thr Ile Ala Arg Asn Ala Asp Gln Glu			
	1365	1370	1375	
15	Glu Leu Val Lys Ile Ser Leu Ser Pro Glu Tyr Val Phe Ser Val Ser			
	1380	1385	1390	
20	Thr Phe Arg Glu Leu Pro Ser Leu Glu Gln Lys Leu Leu Thr Pro Ile			
	1395	1400	1405	
	Thr Thr Leu Thr Ser Glu Gln Ile Gln Lys Leu Leu Ala Ser Thr Arg			
25	1410	1415	1420	
	Tyr Pro Pro Pro Ala Val Glu Ser Asp Ala Ala Asp Ile Val Phe Leu			
	1425	1430	1435	1440
30	Ile Asp Ser Ser Glu Gly Val Arg Pro Asp Gly Phe Ala His Ile Arg			
	1445	1450	1455	
35	Asp Phe Val Ser Arg Ile Val Arg Arg Leu Asn Ile Gly Pro Ser Lys			
	1460	1465	1470	
	Val Arg Val Gly Val Val Gln Phe Ser Asn Asp Val Phe Pro Glu Phe			
40	1475	1480	1485	
	Tyr Leu Lys Thr Tyr Arg Ser Gln Ala Pro Val Leu Asp Ala Ile Arg			
45	1490	1495	1500	
	Arg Leu Arg Leu Arg Gly Gly Ser Pro Leu Asn Thr Gly Lys Ala Leu			
	1505	1510	1515	1520
50	Glu Phe Val Ala Arg Asn Leu Phe Val Lys Ser Ala Gly Ser Arg Ile			
	1525	1530	1535	
	Glu Asp Gly Val Pro Gln His Leu Val Leu Val Leu Gly Gly Lys Ser			
55	1540	1545	1550	

EP 1 439 393 A2

Gln Asp Asp Val Ser Arg Phe Ala Gln Val Ile Arg Ser Ser Gly Ile
1555 1560 1565

5 Val Ser Leu Gly Val Gly Asp Arg Asn Ile Asp Arg Thr Glu Leu Gln
1570 1575 1580

10 Thr Ile Thr Asn Asp Pro Arg Leu Val Phe Thr Val Arg Glu Phe Arg
1585 1590 1595 1600

Glu Leu Pro Asn Ile Glu Glu Arg Ile Met Asn Ser Phe Gly Pro Ser
15 1605 1610 1615

Ala Ala Thr Pro Ala Pro Pro Gly Val Asp Thr Pro Pro Pro Ser Arg
1620 1625 1630

20 Pro Glu Lys Lys Lys Ala Asp Ile Val Phe Leu Leu Asp Gly Ser Ile
1635 1640 1645

25 Asn Phe Arg Arg Asp Ser Phe Gln Glu Val Leu Arg Phe Val Ser Glu
1650 1655 1660

Ile Val Asp Thr Val Tyr Glu Asp Gly Asp Ser Ile Gln Val Gly Leu
30 1665 1670 1675 1680

Val Gln Tyr Asn Ser Asp Pro Thr Asp Glu Phe Phe Leu Lys Asp Phe
35 1685 1690 1695

Ser Thr Lys Arg Gln Ile Ile Asp Ala Ile Asn Lys Val Val Tyr Lys
1700 1705 1710

40 Gly Gly Arg His Ala Asn Thr Lys Val Gly Leu Glu His Leu Arg Val
1715 1720 1725

45 Asn His Phe Val Pro Glu Ala Gly Ser Arg Leu Asp Gln Arg Val Pro
1730 1735 1740

Gln Ile Ala Phe Val Ile Thr Gly Gly Lys Ser Val Glu Asp Ala Gln
50 1745 1750 1755 1760

Asp Val Ser Leu Ala Leu Thr Gln Arg Gly Val Lys Val Phe Ala Val
1765 1770 1775

55 Gly Val Arg Asn Ile Asp Ser Glu Glu Val Gly Lys Ile Ala Ser Asn

EP 1 439 393 A2

	1780	1785	1790	
	Ser Ala Thr Ala Phe Arg Val Gly Asn Val Gln Glu Leu Ser Glu Leu			
5	1795	1800	1805	
	Ser Glu Gln Val Leu Glu Thr Leu His Asp Ala Met His Glu Thr Leu			
10	1810	1815	1820	
	Cys Pro Gly Val Thr Asp Ala Ala Lys Ala Cys Asn Leu Asp Val Ile			
	1825	1830	1835	1840
15	Leu Gly Phe Asp Gly Ser Arg Asp Gln Asn Val Phe Val Ala Gln Lys			
	1845	1850	1855	
20	Gly Phe Glu Ser Lys Val Asp Ala Ile Leu Asn Arg Ile Ser Gln Met			
	1860	1865	1870	
	His Arg Val Ser Cys Ser Gly Gly Arg Ser Pro Thr Val Arg Val Ser			
25	1875	1880	1885	
	Val Val Ala Asn Thr Pro Ser Gly Pro Val Glu Ala Phe Asp Phe Asp			
	1890	1895	1900	
30	Glu Tyr Gln Pro Glu Met Leu Glu Lys Phe Arg Asn Met Arg Ser Gln			
	1905	1910	1915	1920
35	His Pro Tyr Val Leu Thr Glu Asp Thr Leu Lys Val Tyr Leu Asn Lys			
	1925	1930	1935	
	Phe Arg Gln Ser Ser Pro Asp Ser Val Lys Val Val Ile His Phe Thr			
40	1940	1945	1950	
	Asp Gly Ala Asp Gly Asp Leu Ala Asp Leu His Arg Ala Ser Glu Asn			
45	1955	1960	1965	
	Leu Arg Gln Glu Gly Val Arg Ala Leu Ile Leu Val Gly Leu Glu Arg			
	1970	1975	1980	
50	Val Val Asn Leu Glu Arg Leu Met His Leu Glu Phe Gly Arg Gly Phe			
	1985	1990	1995	2000
55	Met Tyr Asp Arg Pro Leu Arg Leu Asn Leu Leu Asp Leu Asp Tyr Glu			
	2005	2010	2015	

EP 1 439 393 A2

Leu Ala Glu Gln Leu Asp Asn Ile Ala Glu Lys Ala Cys Cys Gly Val
2020 2025 2030
5 Pro Cys Lys Cys Ser Gly Gln Arg Gly Asp Arg Gly Pro Ile Gly Ser
2035 2040 2045
10 Ile Gly Pro Lys Gly Ile Pro Gly Glu Asp Gly Tyr Arg Gly Tyr Pro
2050 2055 2060
Gly Asp Glu Gly Gly Pro Gly Glu Arg Gly Pro Pro Gly Val Asn Gly
15 2065 2070 2075 2080
Thr Gln Gly Phe Gln Gly Cys Pro Gly Gln Arg Gly Val Lys Gly Ser
2085 2090 2095
20 Arg Gly Phe Pro Gly Glu Lys Gly Glu Val Gly Glu Ile Gly Leu Asp
2100 2105 2110
25 Gly Leu Asp Gly Glu Asp Gly Asp Lys Gly Leu Pro Gly Ser Ser Gly
2115 2120 2125
Glu Lys Gly Asn Pro Gly Arg Arg Gly Asp Lys Gly Pro Arg Gly Glu
30 2130 2135 2140
Lys Gly Glu Arg Gly Asp Val Gly Ile Arg Gly Asp Pro Gly Asn Pro
35 2145 2150 2155 2160
Gly Gln Asp Ser Gln Glu Arg Gly Pro Lys Gly Glu Thr Gly Asp Leu
2165 2170 2175
40 Gly Pro Met Gly Val Pro Gly Arg Asp Gly Val Pro Gly Gly Pro Gly
2180 2185 2190
45 Glu Thr Gly Lys Asn Gly Gly Phe Gly Arg Arg Gly Pro Pro Gly Ala
2195 2200 2205
Lys Gly Asn Lys Gly Gly Pro Gly Gln Pro Gly Phe Glu Gly Glu Gln
50 2210 2215 2220
Gly Thr Arg Gly Ala Gln Gly Pro Ala Gly Pro Ala Gly Pro Pro Gly
2225 2230 2235 2240
55 Leu Ile Gly Glu Gln Gly Ile Ser Gly Pro Arg Gly Ser Gly Gly Ala

EP 1 439 393 A2

	2245	2250	2255
	Arg Gly Ala Pro Gly Glu Arg Gly Arg Thr Gly Pro Leu Gly Arg Lys		
5	2260	2265	2270
	Gly Glu Pro Gly Glu Pro Gly Pro Lys Gly Gly Ile Gly Asn Pro Gly		
10	2275	2280	2285
	Pro Arg Gly Glu Thr Gly Asp Asp Gly Arg Asp Gly Val Gly Ser Glu		
	2290	2295	2300
15	Gly Arg Arg Gly Lys Lys Gly Glu Arg Gly Phe Pro Gly Tyr Pro Gly		
	2305	2310	2315
	Pro Lys Gly Asn Pro Gly Glu Pro Gly Leu Asn Gly Thr Thr Gly Pro		
20	2325	2330	2335
	Lys Gly Ile Arg Gly Arg Arg Gly Asn Ser Gly Pro Pro Gly Ile Val		
25	2340	2345	2350
	Gly Gln Lys Gly Arg Pro Gly Tyr Pro Gly Pro Ala Gly Pro Arg Gly		
	2355	2360	2365
30	Asn Arg Gly Asp Ser Ile Asp Gln Cys Ala Leu Ile Gln Ser Ile Lys		
	2370	2375	2380
35	Asp Lys Cys Pro Cys Cys Tyr Gly Pro Leu Glu Cys Pro Val Phe Pro		
	2385	2390	2395
	Thr Glu Leu Ala Phe Ala Leu Asp Thr Ser Glu Gly Val Asn Gln Asp		
40	2405	2410	2415
	Thr Phe Gly Arg Met Arg Asp Val Val Leu Ser Ile Val Asn Val Leu		
	2420	2425	2430
45	Thr Ile Ala Glu Ser Asn Cys Pro Thr Gly Ala Arg Val Ala Val Val		
	2435	2440	2445
50	Thr Tyr Asn Asn Glu Val Thr Thr Glu Ile Arg Phe Ala Asp Ser Lys		
	2450	2455	2460
	Arg Lys Ser Val Leu Leu Asp Lys Ile Lys Asn Leu Gln Val Ala Leu		
55	2465	2470	2475
	2480		

EP 1 439 393 A2

	Thr Ser Lys Gln Gln Ser Leu Glu Thr Ala Met Ser Phe Val Ala Arg		
	2485	2490	2495
5	Asn Thr Phe Lys Arg Val Arg Asn Gly Phe Leu Met Arg Lys Val Ala		
	2500	2505	2510
10	Val Phe Phe Ser Asn Thr Pro Thr Arg Ala Ser Pro Gln Leu Arg Glu		
	2515	2520	2525
	Ala Val Leu Lys Leu Ser Asp Ala Gly Ile Thr Pro Leu Phe Leu Thr		
15	2530	2535	2540
	Arg Gln Glu Asp Arg Gln Leu Ile Asn Ala Leu Gln Ile Asn Asn Thr		
	2545	2550	2555
20	Ala Val Gly His Ala Leu Val Leu Pro Ala Gly Arg Asp Leu Thr Asp		
	2565	2570	2575
25	Phe Leu Glu Asn Val Leu Thr Cys His Val Cys Leu Asp Ile Cys Asn		
	2580	2585	2590
	Ile Asp Pro Ser Cys Gly Phe Gly Ser Trp Arg Pro Ser Phe Arg Asp		
30	2595	2600	2605
	Arg Arg Ala Ala Gly Ser Asp Val Asp Ile Asp Met Ala Phe Ile Leu		
	2610	2615	2620
35	Asp Ser Ala Glu Thr Thr Thr Leu Phe Gln Phe Asn Glu Met Lys Lys		
	2625	2630	2635
			2640
40	Tyr Ile Ala Tyr Leu Val Arg Gln Leu Asp Met Ser Pro Asp Pro Lys		
	2645	2650	2655
	Ala Ser Gln His Phe Ala Arg Val Ala Val Val Gln His Ala Pro Ser		
45	2660	2665	2670
	Glu Ser Val Asp Asn Ala Ser Met Pro Pro Val Lys Val Glu Phe Ser		
	2675	2680	2685
50	Leu Thr Asp Tyr Gly Ser Lys Glu Lys Leu Val Asp Phe Leu Ser Arg		
	2690	2695	2700
55	Gly Met Thr Gln Leu Gln Gly Thr Arg Ala Leu Gly Ser Ala Ile Glu		

EP 1 439 393 A2

	2705	2710	2715	2720
	Tyr Thr Ile Glu Asn Val Phe Glu Ser Ala Pro Asn Pro Arg Asp Leu			
5		2725	2730	2735
	Lys Ile Val Val Leu Met Leu Thr Gly Glu Val Pro Glu Gln Gln Leu			
10		2740	2745	2750
	Glu Glu Ala Gln Arg Val Ile Leu Gln Ala Lys Cys Lys Gly Tyr Phe			
	2755	2760	2765	
15	Phe Val Val Leu Gly Ile Gly Arg Lys Val Asn Ile Lys Glu Val Tyr			
	2770	2775	2780	
20	Thr Phe Ala Ser Glu Pro Asn Asp Val Phe Phe Lys Leu Val Asp Lys			
	2785	2790	2795	2800
	Ser Thr Glu Leu Asn Glu Glu Pro Leu Met Arg Phe Gly Arg Leu Leu			
25		2805	2810	2815
	Pro Ser Phe Val Ser Ser Glu Asn Ala Phe Tyr Leu Ser Pro Asp Ile			
	2820	2825	2830	
30	Arg Lys Gln Cys Asp Trp Phe Gln Gly Asp Gln Pro Thr Lys Asn Leu			
	2835	2840	2845	
35	Val Lys Phe Gly His Lys Gln Val Asn Val Pro Asn Asn Val Thr Ser			
	2850	2855	2860	
	Ser Pro Thr Ser Asn Pro Val Thr Thr Thr Lys Pro Val Thr Thr Thr			
40	2865	2870	2875	2880
	Lys Pro Val Thr Thr Thr Thr Lys Pro Val Thr Thr Thr Lys Pro			
45		2885	2890	2895
	Val Thr Ile Ile Asn Gln Pro Ser Val Lys Pro Ala Ala Ala Lys Pro			
	2900	2905	2910	
50	Ala Pro Ala Lys Pro Val Ala Ala Lys Pro Val Ala Thr Lys Thr Ala			
	2915	2920	2925	
	Thr Val Arg Pro Pro Val Ala Val Lys Pro Ala Thr Ala Ala Lys Pro			
55		2930	2935	2940

EP 1 439 393 A2

Val Ala Ala Lys Pro Ala Ala Val Arg Pro Pro Ala Ala Ala Lys
2945 2950 2955 2960
5 Pro Val Ala Thr Lys Pro Glu Val Pro Arg Pro Gln Ala Ala Lys Pro
2965 2970 2975
10 Ala Ala Thr Lys Pro Ala Thr Thr Lys Pro Val Val Lys Met Leu Arg
2980 2985 2990
Glu Val Gln Val Phe Glu Ile Thr Glu Asn Ser Ala Lys Leu His Trp
15 2995 3000 3005
Glu Arg Pro Glu Pro Pro Gly Pro Tyr Phe Tyr Asp Leu Thr Val Thr
20 3010 3015 3020
Ser Ala His Asp Gln Ser Leu Val Leu Lys Gln Asn Leu Thr Val Thr
3025 3030 3035 3040
25 Asp Arg Val Ile Gly Gly Leu Leu Ala Gly Gln Thr Tyr His Val Ala
3045 3050 3055
Val Val Cys Tyr Leu Arg Ser Gln Val Arg Ala Thr Tyr His Gly Ser
30 3060 3065 3070
Phe Ser Thr Lys Lys Ser Gln Pro Pro Pro Pro Gln Pro Ala Arg Ser
35 3075 3080 3085
Ala Ser Ser Ser Thr Ile Asn Leu Met Val Ser Thr Glu Pro Leu Ala
3090 3095 3100
40 Leu Thr Glu Thr Asp Ile Cys Lys Leu Pro Lys Asp Glu Gly Thr Cys
3105 3110 3115 3120
45 Arg Asp Phe Ile Leu Lys Trp Tyr Tyr Asp Pro Asn Thr Lys Ser Cys
3125 3130 3135
Ala Arg Phe Trp Tyr Gly Gly Cys Gly Gly Asn Glu Asn Lys Phe Gly
50 3140 3145 3150
Ser Gln Lys Glu Cys Glu Lys Val Cys Ala Pro Val Leu Ala Lys Pro
3155 3160 3165
55 Gly Val Ile Ser Val Met Gly Thr

3170 3175
 5
 <210> 92
 10 <211> 303
 <212> PRT
 <213> Homo sapiens
 15
 <400> 92
 20 Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
 1 5 10 15
 Ala Ala Pro Gln Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu
 25 20 25 30
 Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val
 35 40 45
 30 Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu
 50 55 60
 35 Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly
 65 70 75 80
 Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln
 40 85 90 95
 Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys
 100 105 110
 45 Ser Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr
 115 120 125
 50 Lys Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp
 130 135 140
 55 Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu
 145 150 155 160

EP 1 439 393 A2

Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val
165 170 175
5 Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln
180 185 190
10 Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala
195 200 205
Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr
15 210 215 220
Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln
225 230 235 240
20 His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg
245 250 255
25 Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr
260 265 270
Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly
30 275 280 285
Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile
35 290 295 300
40 <210> 93
<211> 683
45 <212> PRT
<213> Homo sapiens
50 <400> 93
Met Ala Leu Phe Val Arg Leu Leu Ala Leu Ala Leu Ala Leu Ala Leu
1 5 10 15
55 Gly Pro Ala Ala Thr Leu Ala Gly Pro Ala Lys Ser Pro Tyr Gln Leu

EP 1 439 393 A2

	20	25	30
	Val Leu Gln His Ser Arg Leu Arg Gly Arg Gln His Gly Pro Asn Val		
5	35	40	45
	Cys Ala Val Gln Lys Val Ile Gly Thr Asn Arg Lys Tyr Phe Thr Asn		
10	50	55	60
	Cys Lys Gln Trp Tyr Gln Arg Lys Ile Cys Gly Lys Ser Thr Val Ile		
	65	70	75
15	Ser Tyr Glu Cys Cys Pro Gly Tyr Glu Lys Val Pro Gly Glu Lys Gly		80
	85	90	95
20	Cys Pro Ala Ala Leu Pro Leu Ser Asn Leu Tyr Glu Thr Leu Gly Val		
	100	105	110
	Val Gly Ser Thr Thr Thr Gln Leu Tyr Thr Asp Arg Thr Glu Lys Leu		
25	115	120	125
	Arg Pro Glu Met Glu Gly Pro Gly Ser Phe Thr Ile Phe Ala Pro Ser		
30	130	135	140
	Asn Glu Ala Trp Ala Ser Leu Pro Ala Glu Val Leu Asp Ser Leu Val		
	145	150	155
35	Ser Asn Val Asn Ile Glu Leu Leu Asn Ala Leu Arg Tyr His Met Val		160
	165	170	175
	Gly Arg Arg Val Leu Thr Asp Glu Leu Lys His Gly Met Thr Leu Thr		
40	180	185	190
	Ser Met Tyr Gln Asn Ser Asn Ile Gln Ile His His Tyr Pro Asn Gly		
45	195	200	205
	Ile Val Thr Val Asn Cys Ala Arg Leu Leu Lys Ala Asp His His Ala		
	210	215	220
50	Thr Asn Gly Val Val His Leu Ile Asp Lys Val Ile Ser Thr Ile Thr		
	225	230	235
	Asn Asn Ile Gln Gln Ile Ile Glu Ile Glu Asp Thr Phe Glu Thr Leu		240
55	245	250	255

EP 1 439 393 A2

Arg Ala Ala Val Ala Ala Ser Gly Leu Asn Thr Met Leu Glu Gly Asn
260 265 270
5 Gly Gln Tyr Thr Leu Leu Ala Pro Thr Asn Glu Ala Phe Glu Lys Ile
275 280 285
10 Pro Ser Glu Thr Leu Asn Arg Ile Leu Gly Asp Pro Glu Ala Leu Arg
290 295 300
Asp Leu Leu Asn Asn His Ile Leu Lys Ser Ala Met Cys Ala Glu Ala
15 305 310 315 320
Ile Val Ala Gly Leu Ser Val Glu Thr Leu Glu Gly Thr Thr Leu Glu
20 325 330 335
Val Gly Cys Ser Gly Asp Met Leu Thr Ile Asn Gly Lys Ala Ile Ile
340 345 350
25 Ser Asn Lys Asp Ile Leu Ala Thr Asn Gly Val Ile His Tyr Ile Asp
355 360 365
Glu Leu Leu Ile Pro Asp Ser Ala Lys Thr Leu Phe Glu Leu Ala Ala
30 370 375 380
Glu Ser Asp Val Ser Thr Ala Ile Asp Leu Phe Arg Gln Ala Gly Leu
35 385 390 395 400
Gly Asn His Leu Ser Gly Ser Glu Arg Leu Thr Leu Leu Ala Pro Leu
405 410 415
40 Asn Ser Val Phe Lys Asp Gly Thr Pro Pro Ile Asp Ala His Thr Arg
420 425 430
45 Asn Leu Leu Arg Asn His Ile Ile Lys Asp Gln Leu Ala Ser Lys Tyr
435 440 445
Leu Tyr His Gly Gln Thr Leu Glu Thr Leu Gly Gly Lys Lys Leu Arg
50 450 455 460
Val Phe Val Tyr Arg Asn Ser Leu Cys Ile Glu Asn Ser Cys Ile Ala
465 470 475 480
55 Ala His Asp Lys Arg Gly Arg Tyr Gly Thr Leu Phe Thr Met Asp Arg

EP 1 439 393 A2

	485	490	495
5	Val Leu Thr Pro Pro Met Gly Thr Val Met Asp Val Leu Lys Gly Asp		
	500	505	510
10	Asn Arg Phe Ser Met Leu Val Ala Ala Ile Gln Ser Ala Gly Leu Thr		
	515	520	525
	Glu Thr Leu Asn Arg Glu Gly Val Tyr Thr Val Phe Ala Pro Thr Asn		
	530	535	540
15	Glu Ala Phe Arg Ala Leu Pro Pro Arg Glu Arg Ser Arg Leu Leu Gly		
	545	550	555
20	Asp Ala Lys Glu Leu Ala Asn Ile Leu Lys Tyr His Ile Gly Asp Glu		
	565	570	575
	Ile Leu Val Ser Gly Gly Ile Gly Ala Leu Val Arg Leu Lys Ser Leu		
25	580	585	590
	Gln Gly Asp Lys Leu Glu Val Ser Leu Lys Asn Asn Val Val Ser Val		
	595	600	605
30	Asn Lys Glu Pro Val Ala Glu Pro Asp Ile Met Ala Thr Asn Gly Val		
	610	615	620
35	Val His Val Ile Thr Asn Val Leu Gln Pro Pro Ala Asn Arg Pro Gln		
	625	630	635
	Glu Arg Gly Asp Glu Leu Ala Asp Ser Ala Leu Glu Ile Phe Lys Gln		
40	645	650	655
	Ala Ser Ala Phe Ser Arg Ala Ser Gln Arg Ser Val Arg Leu Ala Pro		
45	660	665	670
	Val Tyr Gln Lys Leu Leu Glu Arg Met Lys His		
	675	680	
50			
55	<210> 94		
	<211> 2355		

<212> PRT

<213> Homo sapiens

5

<400> 94

10 Met Leu Arg Gly Pro Gly Pro Gly Leu Leu Leu Leu Ala Val Gln Cys
 1 5 10 15
 Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg Gln
 15 20 25 30
 Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser
 20 35 40 45
 Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
 50 55 60
 25 Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
 65 70 75 80
 Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
 30 85 90 95
 Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
 35 100 105 110
 Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
 115 120 125
 40 Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly
 130 135 140
 Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
 45 145 150 155 160
 Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu
 50 165 170 175
 Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
 180 185 190
 55 Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp

EP 1 439 393 A2

	195	200	205
	Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr		
5	210	215	220
	Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr		
10	225	230	235
	Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu		
	245	250	255
15	Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg		
	260	265	270
20	His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp		
	275	280	285
	Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro		
25	290	295	300
	Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met		
30	305	310	315
	Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu		
	325	330	335
35	Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly		
	340	345	350
	Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly		
40	355	360	365
	Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu		
45	370	375	380
	Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe		
	385	390	395
50	Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser Asn		
	405	410	415
	Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr		
55	420	425	430

EP 1 439 393 A2

	Asp	Cys	Thr	Ser	Glu	Gly	Arg	Arg	Asp	Asn	Met	Lys	Trp	Cys	Gly	Thr
	435								440							445
5	Thr	Gln	Asn	Tyr	Asp	Ala	Asp	Gln	Lys	Phe	Gly	Phe	Cys	Pro	Met	Ala
	450							455					460			
10	Ala	His	Glu	Glu	Ile	Cys	Thr	Thr	Asn	Glu	Gly	Val	Met	Tyr	Arg	Ile
	465					470					475					480
	Gly	Asp	Gln	Trp	Asp	Lys	Gln	His	Asp	Met	Gly	His	Met	Met	Arg	Cys
15						485				490						495
	Thr	Cys	Val	Gly	Asn	Gly	Arg	Gly	Glu	Trp	Thr	Cys	Ile	Ala	Tyr	Ser
20			500						505					510		
	Gln	Leu	Arg	Asp	Gln	Cys	Ile	Val	Asp	Asp	Ile	Thr	Tyr	Asn	Val	Asn
	515							520					525			
25	Asp	Thr	Phe	His	Lys	Arg	His	Glu	Glu	Gly	His	Met	Leu	Asn	Cys	Thr
	530						535					540				
	Cys	Phe	Gly	Gln	Gly	Arg	Gly	Arg	Trp	Lys	Cys	Asp	Pro	Val	Asp	Gln
30	545					550					555					560
	Cys	Gln	Asp	Ser	Glu	Thr	Gly	Thr	Phe	Tyr	Gln	Ile	Gly	Asp	Ser	Trp
35					565					570						575
	Glu	Lys	Tyr	Val	His	Gly	Val	Arg	Tyr	Gln	Cys	Tyr	Cys	Tyr	Gly	Arg
40					580					585				590		
	Gly	Ile	Gly	Glu	Trp	His	Cys	Gln	Pro	Leu	Gln	Thr	Tyr	Pro	Ser	Ser
	595							600					605			
45	Ser	Gly	Pro	Val	Glu	Val	Phe	Ile	Thr	Glu	Thr	Pro	Ser	Gln	Pro	Asn
	610						615					620				
	Ser	His	Pro	Ile	Gln	Trp	Asn	Ala	Pro	Gln	Pro	Ser	His	Ile	Ser	Lys
50	625					630					635					640
	Tyr	Ile	Leu	Arg	Trp	Arg	Pro	Lys	Asn	Ser	Val	Gly	Arg	Trp	Lys	Glu
55					645					650						655
	Ala	Thr	Ile	Pro	Gly	His	Leu	Asn	Ser	Tyr	Thr	Ile	Lys	Gly	Leu	Lys

EP 1 439 393 A2

	660		665		670
5	Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser Ile Gln Gln Tyr Gly				
	675		680		685
	His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr Thr Ser Thr Ser Thr				
10	690		695		700
	Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr Thr Pro Phe Ser Pro				
	705		710		715
15	Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile Thr Ala Ser Ser Phe				
	725		730		735
20	Val Val Ser Trp Val Ser Ala Ser Asp Thr Val Ser Gly Phe Arg Val				
	740		745		750
	Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro Gln Tyr Leu Asp Leu				
25	755		760		765
	Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp Leu Leu Pro Gly Arg				
30	770		775		780
	Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu Asp Gly Glu Gln Ser				
	785		790		795
35	Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro Asp Ala Pro Pro Asp				
	805		810		815
	Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile Val Val Arg Trp Ser				
40	820		825		830
	Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile Val Tyr Ser Pro Ser				
45	835		840		845
	Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn Ser				
	850		855		860
50	Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr Ile				
	865		870		875
					880
55	Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln Gln				
	885		890		895

EP 1 439 393 A2

Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg Asp
 900 905 910
 5 Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp Thr
 915 920 925
 10 Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val
 930 935 940
 Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn Thr
 15 945 950 955 960
 Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys
 965 970 975
 20 Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala Gln
 980 985 990
 25 Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu
 995 1000 1005
 Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln Ile
 30 1010 1015 1020
 Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln Pro Arg
 35 1025 1030 1035 1040
 Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr Pro Leu Arg Asn Leu
 1045 1050 1055
 40 Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala Ile Lys Gly Asn
 1060 1065 1070
 45 Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr Thr Leu Gln Pro Gly
 1075 1080 1085
 Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr Glu Thr Thr Ile Val
 50 1090 1095 1100
 Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe Lys Leu Gly Val Arg
 1105 1110 1115 1120
 55 Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly

EP 1 439 393 A2

	1125	1130	1135
5	Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr		
	1140	1145	1150
	Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp Ala Pro Ile Val Asn		
10	1155	1160	1165
	Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala		
	1170	1175	1180
15	Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr		
	1185	1190	1195
	Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln		
20	1205	1210	1215
	Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys		
25	1220	1225	1230
	Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr		
	1235	1240	1245
30	Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile Ile		
	1250	1255	1260
35	Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe Thr Asn Ile Gly Pro		
	1265	1270	1275
	Asp Thr Met Arg Val Thr Trp Ala Pro Pro Pro Ser Ile Asp Leu Thr		
40	1285	1290	1295
	Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn Glu Glu Asp Val Ala		
45	1300	1305	1310
	Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val Val Leu Thr Asn Leu		
	1315	1320	1325
50	Leu Pro Gly Thr Glu Tyr Val Val Ser Val Ser Ser Val Tyr Glu Gln		
	1330	1335	1340
55	His Glu Ser Thr Pro Leu Arg Gly Arg Gln Lys Thr Gly Leu Asp Ser		
	1345	1350	1355
			1360

EP 1 439 393 A2

Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val
1365 1370 1375
5 His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr Arg Ile Arg His
1380 1385 1390
10 His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His
1395 1400 1405
Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro Gly Thr Glu Tyr
15 1410 1415 1420
Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu
1425 1430 1435 1440
20 Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg Asp Leu Glu Val
1445 1450 1455
25 Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala
1460 1465 1470
Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
30 1475 1480 1485
Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys Ser Thr Ala Thr
35 1490 1495 1500
Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
1505 1510 1515 1520
40 Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile
1525 1530 1535
45 Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln Met Gln Val Thr Asp
1540 1545 1550
Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu Pro Ser Ser Ser Pro
50 1555 1560 1565
Val Thr Gly Tyr Arg Val Thr Thr Thr Pro Lys Asn Gly Pro Gly Pro
1570 1575 1580
55 Thr Lys Thr Lys Thr Ala Gly Pro Asp Gln Thr Glu Met Thr Ile Glu

EP 1 439 393 A2

	1585	1590	1595	1600
	Gly	Leu	Gln	Pro Thr Val Glu Tyr Val Val Ser Val Tyr Ala Gln Asn
5		1605	1610	1615
	Pro	Ser Gly Glu Ser Gln Pro Leu Val Gln Thr Ala Val Thr Asn Ile		
10		1620	1625	1630
	Asp	Arg Pro Lys Gly Leu Ala Phe Thr Asp Val Asp Val Asp Ser Ile		
	1635	1640	1645	
15	Lys	Ile Ala Trp Glu Ser Pro Gln Gly Gln Val Ser Arg Tyr Arg Val		
	1650	1655	1660	
20	Thr	Tyr Ser Ser Pro Glu Asp Gly Ile His Glu Leu Phe Pro Ala Pro		
	1665	1670	1675	1680
	Asp	Gly Glu Glu Asp Thr Ala Glu Leu Gln Gly Leu Arg Pro Gly Ser		
25		1685	1690	1695
	Glu	Tyr Thr Val Ser Val Val Ala Leu His Asp Asp Met Glu Ser Gln		
	1700	1705	1710	
30	Pro	Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro Ala Pro Thr Asp Leu		
	1715	1720	1725	
35	Lys	Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro		
	1730	1735	1740	
	Pro	Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu		
40	1745	1750	1755	1760
	Lys	Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser		
45		1765	1770	1775
	Val	Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val		
	1780	1785	1790	
50	Tyr	Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val		
	1795	1800	1805	
55	Thr	Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp		
	1810	1815	1820	

EP 1 439 393 A2

	Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr	
	1825	1830 1835 1840
5	Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro	
	1845	1850 1855
10	Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly	
	1860	1865 1870
	Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp	
15	1875	1880 1885
	Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp	
20	1890	1895 1900
	Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu	
	1905	1910 1915 1920
25	Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys	
	1925	1930 1935
30	Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg	
	1940	1945 1950
	Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu	
35	1955	1960 1965
	Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro	
	1970	1975 1980
40	Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro Gln Leu Val Thr Leu	
	1985	1990 1995 2000
45	Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val Pro Ser Thr	
	2005	2010 2015
	Val Gln Lys Thr Pro Phe Val Thr His Pro Gly Tyr Asp Thr Gly Asn	
50	2020	2025 2030
	Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln Pro Ser Val Gly Gln	
	2035	2040 2045
55	Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg Thr Thr Pro Pro Thr	

EP 1 439 393 A2

	2050	2055	2060
	Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro Tyr Pro Pro Asn Val		
5	2065	2070	2075 2080
	Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser Trp Ala Pro Phe Gln		
10	2085	2090	2095
	Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro Val Gly Thr Asp Glu		
	2100	2105	2110
15	Glu Pro Leu Gln Phe Arg Val Pro Gly Thr Ser Thr Ser Ala Thr Leu		
	2115	2120	2125
20	Thr Gly Leu Thr Arg Gly Ala Thr Tyr Asn Ile Ile Val Glu Ala Leu		
	2130	2135	2140
	Lys Asp Gln Gln Arg His Lys Val Arg Glu Glu Val Val Thr Val Gly		
25	2145	2150	2155 2160
	Asn Ser Val Asn Glu Gly Leu Asn Gln Pro Thr Asp Asp Ser Cys Phe		
	2165	2170	2175
30	Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly Asp Glu Trp Glu Arg		
	2180	2185	2190
35	Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe Gly		
	2195	2200	2205
	Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp Asn Gly		
40	2210	2215	2220
	Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly		
45	2225	2230	2235 2240
	Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys		
	2245	2250	2255
50	Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His		
	2260	2265	2270
55	Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys		
	2275	2280	2285

EP 1 439 393 A2

Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg
2290 2295 2300
5 Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn
2305 2310 2315 2320
10 Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys
2325 2330 2335
Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp
15 2340 2345 2350
Ser Arg Glu
20 2355
25 <210> 95
<211> 1366
<212> PRT
30 <213> Homo sapiens
35 <400> 95
Met Leu Ser Phe Val Asp Thr Arg Thr Leu Leu Leu Leu Ala Val Thr
1 5 10 15
40 Leu Cys Leu Ala Thr Cys Gln Ser Leu Gln Glu Glu Thr Val Arg Lys
20 25 30
45 Gly Pro Ala Gly Asp Arg Gly Pro Arg Gly Glu Arg Gly Pro Pro Gly
35 40 45
Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro
50 50 55 60
Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln
55 65 70 75 80
Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met

EP 1 439 393 A2

	85	90	95
5	Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly		
	100	105	110
10	Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro		
	115	120	125
	Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp		
15	130	135	140
	Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly		
	145	150	155
20	Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe		
	165	170	175
	Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro		
25	180	185	190
	Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly		
30	195	200	205
	Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg		
	210	215	220
35	Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val		
	225	230	235
	Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly		
40	245	250	255
	Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn		
45	260	265	270
	Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro		
	275	280	285
50	Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly		
	290	295	300
55	Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala		
	305	310	315
			320

EP 1 439 393 A2

Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala
325 330 335
5 Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly
340 345 350
10 Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro
355 360 365
Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
15 370 375 380
Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
20 385 390 395 400
Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val
405 410 415
25 Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg
420 425 430
Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
30 435 440 445
Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys
35 450 455 460
Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile
465 470 475 480
40 Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly
485 490 495
45 Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His
500 505 510
Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
50 515 520 525
Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
530 535 540
55 Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro

EP 1 439 393 A2

	545	550	555	560
	Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His			
5		565	570	575
	Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly			
10		580	585	590
	Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser			
	595	600	605	
15	Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro			
	610	615	620	
20	Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly			
	625	630	635	640
	Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu			
25		645	650	655
	Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp			
	660	665	670	
30	Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly			
	675	680	685	
35	Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro			
	690	695	700	
	Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala			
40	705	710	715	720
	Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly			
45		725	730	735
	Ala Lys Gly Glu Arg Gly Ala Lys Gly Pro Lys Gly Glu Asn Gly Val			
	740	745	750	
50	Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn			
	755	760	765	
55	Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly			
	770	775	780	

EP 1 439 393 A2

	Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro
	785 790 795 800
5	Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu
	805 810 815
10	Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly
	820 825 830
	Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro
15	835 840 845
	Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln
20	850 855 860
	Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly
	865 870 875 880
25	Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro
	885 890 895
	Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val
30	900 905 910
	Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly
35	915 920 925
	Asn Pro Gly Asn Asp Gly Pro Pro Gly Arg Asp Gly Gln Pro Gly His
	930 935 940
40	Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala
	945 950 955 960
45	Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly
	965 970 975
	Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala
50	980 985 990
	Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys
	995 1000 1005
55	Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly

EP 1 439 393 A2

	1010	1015	1020
	His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp		
5	1025	1030	1035 1040
	Gln Gly Ala Pro Gly Ser Val Gly Pro Ala Gly Pro Arg Gly Pro Ala		
10	1045	1050	1055
	Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly His Pro Gly		
	1060	1065	1070
15	Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro		
	1075	1080	1085
20	Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser		
	1090	1095	1100
	Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp		
25	1105	1110	1115 1120
	Gln Pro Arg Ser Ala Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp		
	1125	1130	1135
30	Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro		
	1140	1145	1150
35	Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu		
	1155	1160	1165
	Ser His Pro Glu Trp Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln		
40	1170	1175	1180
	Gly Cys Thr Met Asp Ala Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly		
45	1185	1190	1195 1200
	Glu Thr Cys Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp		
	1205	1210	1215
50	Tyr Arg Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile		
	1220	1225	1230
	Asn Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys		
55	1235	1240	1245

EP 1 439 393 A2

Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala
 1250 1255 1260
 5 Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp
 1265 1270 1275 1280
 10 Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn
 1285 1290 1295
 Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val
 15 1300 1305 1310
 Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile
 20 1315 1320 1325
 Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile
 1330 1335 1340
 25 Ala Pro Leu Asp Ile Gly Gly Ala Asp His Glu Phe Phe Val Asp Ile
 1345 1350 1355 1360
 30 Gly Pro Val Cys Phe Lys
 1365
 35
 <210> 96
 <211> 105
 40 <212> PRT
 <213> Homo sapiens
 45
 <400> 96
 Met Ala Lys Ile Ser Ser Pro Thr Glu Thr Glu Arg Cys Ile Glu Ser
 50 1 5 10 15
 Leu Ile Ala Val Phe Gln Lys Tyr Ala Gly Lys Asp Gly Tyr Asn Tyr
 55 20 25 30
 Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Thr Glu Leu Ala

EP 1 439 393 A2

35 40 45
 5 Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met
 50 55 60
 Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe
 10 65 70 75 80
 Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu
 85 90 95
 15 Lys Ala Val Pro Ser Gln Lys Arg Thr
 100 105
 20
 <210> 97
 25 <211> 283
 <212> PRT
 30 <213> Homo sapiens
 <400> 97
 35 Met Val Asn Tyr Ala Trp Ala Gly Arg Ser Gln Arg Lys Leu Trp Trp
 1 5 10 15
 Arg Ser Val Ala Val Leu Thr Cys Lys Ser Val Val Arg Pro Gly Tyr
 40 20 25 30
 Arg Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu Lys Thr Cys Ala
 45 35 40 45
 Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys Met Val Ala Pro Trp
 50 55 60
 50 Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu Cys Cys His Val Arg Thr
 65 70 75 80
 Gly Thr Ile Leu Leu Gly Val Trp Tyr Leu Ile Ile Asn Ala Val Val
 55 85 90 95

EP 1 439 393 A2

Leu Leu Ile Leu Leu Ser Ala Leu Ala Asp Pro Asp Gln Tyr Asn Phe
 100 105 110
 5 Ser Ser Ser Glu Leu Gly Gly Asp Phe Glu Phe Met Asp Asp Ala Asn
 115 120 125
 10 Met Cys Ile Ala Ile Ala Ile Ser Leu Leu Met Ile Leu Ile Cys Ala
 130 135 140
 Met Ala Thr Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile Ile Pro
 15 145 150 155 160
 Phe Phe Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala
 165 170 175
 20 Ile Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile Arg Gln
 180 185 190
 25 Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val Asn Pro
 195 200 205
 Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile Leu Thr
 30 210 215 220
 Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg Tyr Ile
 35 225 230 235 240
 Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val Thr Ser Asn Asp
 245 250 255
 40 Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn Gly Ala
 260 265 270
 45 Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala
 275 280
 50
 <210> 98
 <211> 712
 55 <212> PRT

<213> Homo sapiens

5

<400> 98

Met Ala Gly Gly Pro Gly Pro Gly Glu Pro Ala Ala Pro Gly Ala Gln

10

1

5

10

15

His Phe Leu Tyr Glu Val Pro Pro Trp Val Met Cys Arg Phe Tyr Lys

20

25

30

15

Val Met Asp Ala Leu Glu Pro Ala Asp Trp Cys Gln Phe Ala Ala Leu

35

40

45

20

Ile Val Arg Asp Gln Thr Glu Leu Arg Leu Cys Glu Arg Ser Gly Gln

50

55

60

Arg Thr Ala Ser Val Leu Trp Pro Trp Ile Asn Arg Asn Ala Arg Val

25

65

70

75

80

Ala Asp Leu Val His Ile Leu Thr His Leu Gln Leu Leu Arg Ala Arg

85

90

95

30

Asp Ile Ile Thr Ala Trp His Pro Pro Ala Pro Leu Pro Ser Pro Gly

100

105

110

35

Thr Thr Ala Pro Arg Pro Ser Ser Ile Pro Ala Pro Ala Glu Ala Glu

115

120

125

Ala Trp Ser Pro Arg Lys Leu Pro Ser Ser Ala Ser Thr Phe Leu Ser

40

130

135

140

Pro Ala Phe Pro Gly Ser Gln Thr His Ser Gly Pro Glu Leu Gly Leu

45

145

150

155

160

Val Pro Ser Pro Ala Ser Leu Trp Pro Pro Pro Pro Ser Pro Ala Pro

165

170

175

50

Ser Ser Thr Lys Pro Gly Pro Glu Ser Ser Val Ser Leu Leu Gln Gly

180

185

190

55

Ala Arg Pro Ser Pro Phe Cys Trp Pro Leu Cys Glu Ile Ser Arg Gly

195

200

205

EP 1 439 393 A2

Thr His Asn Phe Ser Glu Glu Leu Lys Ile Gly Glu Gly Gly Phe Gly
 210 215 220
 5 Cys Val Tyr Arg Ala Val Met Arg Asn Thr Val Tyr Ala Val Lys Arg
 225 230 235 240
 10 Leu Lys Glu Asn Ala Asp Leu Glu Trp Thr Ala Val Lys Gln Ser Phe
 245 250 255
 Leu Thr Glu Val Glu Gln Leu Ser Arg Phe Arg His Pro Asn Ile Val
 15 260 265 270
 Asp Phe Ala Gly Tyr Cys Ala Gln Asn Gly Phe Tyr Cys Leu Val Tyr
 275 280 285
 20 Gly Phe Leu Pro Asn Gly Ser Leu Glu Asp Arg Leu His Cys Gln Thr
 290 295 300
 25 Gln Ala Cys Pro Pro Leu Ser Trp Pro Gln Arg Leu Asp Ile Leu Leu
 305 310 315 320
 Gly Thr Ala Arg Ala Ile Gln Phe Leu His Gln Asp Ser Pro Ser Leu
 30 325 330 335
 Ile His Gly Asp Ile Lys Ser Ser Asn Val Leu Leu Asp Glu Arg Leu
 35 340 345 350
 Thr Pro Lys Leu Gly Asp Phe Gly Leu Ala Arg Phe Ser Arg Phe Ala
 355 360 365
 40 Gly Ser Ser Pro Ser Gln Ser Ser Met Val Ala Arg Thr Gln Thr Val
 370 375 380
 45 Arg Gly Thr Leu Ala Tyr Leu Pro Glu Glu Tyr Ile Lys Thr Gly Arg
 385 390 395 400
 Leu Ala Val Asp Thr Asp Thr Phe Ser Phe Gly Val Val Val Leu Glu
 50 405 410 415
 Thr Leu Ala Gly Gln Arg Ala Val Lys Thr His Gly Ala Arg Thr Lys
 420 425 430
 55 Tyr Leu Lys Asp Leu Val Glu Glu Glu Ala Glu Glu Ala Gly Val Ala

EP 1 439 393 A2

	435	440	445
5	Leu Arg Ser Thr Gln Ser Thr	Leu Gln Ala Gly Leu Ala Ala Asp Ala	
	450	455	460
	Trp Ala Ala Pro Ile Ala Met Gln Ile Tyr Lys Lys His Leu Asp Pro		
10	465	470	475 480
	Arg Pro Gly Pro Cys Pro Pro Glu Leu Gly Leu Gly Leu Gly Gln Leu		
	485	490	495
15	Ala Cys Cys Cys Leu His Arg Arg Ala Lys Arg Arg Pro Pro Met Thr		
	500	505	510
20	Gln Val Tyr Glu Arg Leu Glu Lys Leu Gln Ala Val Val Ala Gly Val		
	515	520	525
	Pro Gly His Leu Glu Ala Ala Ser Cys Ile Pro Pro Ser Pro Gln Glu		
25	530	535	540
	Asn Ser Tyr Val Ser Ser Thr Gly Arg Ala His Ser Gly Ala Ala Pro		
30	545	550	555 560
	Trp Gln Pro Leu Ala Ala Pro Ser Gly Ala Ser Ala Gln Ala Ala Glu		
	565	570	575
35	Gln Leu Gln Arg Gly Pro Asn Gln Pro Val Glu Ser Asp Glu Ser Leu		
	580	585	590
40	Gly Gly Leu Ser Ala Ala Leu Arg Ser Trp His Leu Thr Pro Ser Cys		
	595	600	605
	Pro Leu Asp Pro Ala Pro Leu Arg Glu Ala Gly Cys Pro Gln Gly Asp		
45	610	615	620
	Thr Ala Gly Glu Ser Ser Trp Gly Ser Gly Pro Gly Ser Arg Pro Thr		
	625	630	635 640
50	Ala Val Glu Gly Leu Ala Leu Gly Ser Ser Ala Ser Ser Ser Ser Glu		
	645	650	655
55	Pro Pro Gln Ile Ile Ile Asn Pro Ala Arg Gln Lys Met Val Gln Lys		
	660	665	670

Leu Ala Leu Tyr Glu Asp Gly Ala Leu Asp Ser Leu Gln Leu Leu Ser
 5 675 680 685
 Ser Ser Ser Leu Pro Gly Leu Gly Leu Glu Gln Asp Arg Gln Gly Pro
 690 695 700
 10 Glu Glu Ser Asp Glu Phe Gln Ser
 705 710
 15
 <210> 99
 20 <211> 132
 <212> PRT
 <213> Homo sapiens
 25
 <400> 99
 30 Met Asn His Ile Val Gln Thr Phe Ser Pro Val Asn Ser Gly Gln Pro
 1 5 10 15
 Pro Asn Tyr Glu Met Leu Lys Glu Glu Gln Glu Val Ala Met Leu Gly
 35 20 25 30
 Gly Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile Arg
 35 40 45
 40 Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr
 50 55 60
 45 Leu Phe Met Asn Thr Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser
 65 70 75 80
 Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln
 50 85 90 95
 Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu
 100 105 110
 55 Gly Ile Phe Met Thr Ile Leu Leu Val Ile Ile Pro Val Leu Val Val

EP 1 439 393 A2

115 120 125
 5 Gln Ala Gln Arg
 130
 10
 <210> 100
 15 <211> 207
 <212> PRT
 <213> Homo sapiens
 20
 <400> 100
 25 Met Ala Pro Phe Glu Pro Leu Ala Ser Gly Ile Leu Leu Leu Leu Trp
 1 5 10 15
 Leu Ile Ala Pro Ser Arg Ala Cys Thr Cys Val Pro Pro His Pro Gln
 30 20 25 30
 Thr Ala Phe Cys Asn Ser Asp Leu Val Ile Arg Ala Lys Phe Val Gly
 35 35 40 45
 Thr Pro Glu Val Asn Gln Thr Thr Leu Tyr Gln Arg Tyr Glu Ile Lys
 50 55 60
 40 Met Thr Lys Met Tyr Lys Gly Phe Gln Ala Leu Gly Asp Ala Ala Asp
 65 70 75 80
 Ile Arg Phe Val Tyr Thr Pro Ala Met Glu Ser Val Cys Gly Tyr Phe
 45 85 90 95
 His Arg Ser His Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu
 100 105 110
 50 Gln Asp Gly Leu Leu His Ile Thr Thr Cys Ser Phe Val Ala Pro Trp
 115 120 125
 55 Asn Ser Leu Ser Leu Ala Gln Arg Arg Gly Phe Thr Lys Thr Tyr Thr
 130 135 140

Val Gly Cys Glu Glu Cys Thr Val Phe Pro Cys Leu Ser Ile Pro Cys
 5 145 150 155 160
 Lys Leu Gln Ser Gly Thr His Cys Leu Trp Thr Asp Gln Leu Leu Gln
 165 170 175
 10 Gly Ser Glu Lys Gly Phe Gln Ser Arg His Leu Ala Cys Leu Pro Arg
 180 185 190
 15 Glu Pro Gly Leu Cys Thr Trp Gln Ser Leu Arg Ser Gln Ile Ala
 195 200 205
 20
 <210> 101
 <211> 282
 25 <212> PRT
 <213> Homo sapiens
 30
 <400> 101
 Met Glu Arg Pro Ser Leu Arg Ala Leu Leu Leu Gly Ala Ala Gly Leu
 35 1 5 10 15
 Leu Leu Leu Leu Leu Pro Leu Ser Ser Ser Ser Ser Ser Asp Thr Cys
 20 25 30
 40 Gly Pro Cys Glu Pro Ala Ser Cys Pro Pro Leu Pro Pro Leu Gly Cys
 35 40 45
 45 Leu Leu Gly Glu Thr Arg Asp Ala Cys Gly Cys Cys Pro Met Cys Ala
 50 55 60
 Arg Gly Glu Gly Glu Pro Cys Gly Gly Gly Gly Ala Gly Arg Gly Tyr
 50 65 70 75 80
 Cys Ala Pro Gly Met Glu Cys Val Lys Ser Arg Lys Arg Arg Lys Gly
 85 90 95
 55 Lys Ala Gly Ala Ala Ala Gly Gly Pro Gly Val Ser Gly Val Cys Val

5 100 105 110
 Cys Lys Ser Arg Tyr Pro Val Cys Gly Ser Asp Gly Thr Thr Tyr Pro
 115 120 125
 10 Ser Gly Cys Gln Leu Arg Ala Ala Ser Gln Arg Ala Glu Ser Arg Gly
 130 135 140
 Glu Lys Ala Ile Thr Gln Val Ser Lys Gly Thr Cys Glu Gln Gly Pro
 15 145 150 155 160
 Ser Ile Val Thr Pro Pro Lys Asp Ile Trp Asn Val Thr Gly Ala Gln
 165 170 175
 20 Val Tyr Leu Ser Cys Glu Val Ile Gly Ile Pro Thr Pro Val Leu Ile
 180 185 190
 25 Trp Asn Lys Val Lys Arg Gly His Tyr Gly Val Gln Arg Thr Glu Leu
 195 200 205
 Leu Pro Gly Asp Arg Asp Asn Leu Ala Ile Gln Thr Arg Gly Gly Pro
 30 210 215 220
 Glu Lys His Glu Val Thr Gly Trp Val Leu Val Ser Pro Leu Ser Lys
 225 230 235 240
 35 Glu Asp Ala Gly Glu Tyr Glu Cys His Ala Ser Asn Ser Gln Gly Gln
 245 250 255
 40 Ala Ser Ala Ser Ala Lys Ile Thr Val Val Asp Ala Leu His Glu Ile
 260 265 270
 Pro Val Lys Lys Gly Glu Gly Ala Glu Leu
 45 275 280

 50 <210> 102
 <211> 125
 <212> PRT
 55 <213> Homo sapiens

5 <400> 102

Met His Lys Glu Glu His Glu Val Ala Val Leu Gly Ala Pro Pro Ser

1 5 10 15

10 Thr Ile Leu Pro Arg Ser Thr Val Ile Asn Ile His Ser Glu Thr Ser

20 25 30

15 Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr Leu Phe Leu Asn

35 40 45

Trp Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser Val Lys Ser Arg

20 50 55 60

Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln Ala Tyr Ala Ser

65 70 75 80

25 Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu Gly Ile Leu Met

85 90 95

30 Thr Ile Gly Phe Ile Leu Leu Leu Val Phe Gly Ser Val Thr Val Tyr

100 105 110

His Ile Met Leu Gln Ile Ile Gln Glu Lys Arg Gly Tyr

35 115 120 125

40 <210> 103

<211> 1466

45 <212> PRT

<213> Homo sapiens

50 <400> 103

Met Met Ser Phe Val Gln Lys Gly Ser Trp Leu Leu Leu Ala Leu Leu

1 5 10 15

55 His Pro Thr Ile Ile Leu Ala Gln Gln Glu Ala Val Glu Gly Gly Cys

	20	25	30
5	Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu		
	35	40	45
	Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp		
10	50	55	60
	Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro		
	65	70	75
15	Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr		
	85	90	95
20	Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly		
	100	105	110
	Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln		
25	115	120	125
	Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys		
30	130	135	140
	Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val		
	145	150	155
35	Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala		
	165	170	175
	Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly		
40	180	185	190
	Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln		
45	195	200	205
	Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser		
	210	215	220
50	Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly		
	225	230	235
	Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile		
55	245	250	255

EP 1 439 393 A2

Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
5 260 265 270

Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
 275 280 285

10 Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
 290 295 300

15 Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
305 310 315 320

Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
20 325 330 335

Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
 340 345 350

25 Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg
 355 360 365

30 Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly
370 375 380

Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro
35 385 390 395 400

Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro
 405 410 415

40 Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly
 420 425 430

45 Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu
 435 440 445

Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp
50 450 455 460

Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly
465 470 475 480

55 Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro

EP 1 439 393 A2

	485	490	495
5	Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro		
	500	505	510
	Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly		
10	515	520	525
	Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly		
	530	535	540
15	Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser		
	545	550	555
	Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly		
20	565	570	575
	Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys		
25	580	585	590
	Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro		
	595	600	605
30	Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly		
	610	615	620
35	Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu		
	625	630	635
	Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro		
40	645	650	655
	Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly		
45	660	665	670
	Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu		
	675	680	685
50	Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu		
	690	695	700
	Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly		
55	705	710	715
			720

Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser
 725 730 735
 5 Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp
 740 745 750
 10 Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
 755 760 765
 Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala
 15 770 775 780
 Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg
 20 785 790 795 800
 Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
 805 810 815
 25 Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu
 820 825 830
 Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser
 30 835 840 845
 Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly
 35 850 855 860
 Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu
 865 870 875 880
 40 Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
 885 890 895
 Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly
 45 900 905 910
 Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln
 50 915 920 925
 Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro
 930 935 940
 55 Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly

EP 1 439 393 A2

	945	950	955	960
5	Pro Pro Gly Met	Pro Gly Pro Arg Gly Ser	Pro Gly Pro Gln Gly Val	
	965	970	975	
	Lys Gly Glu Ser Gly Lys	Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg		
10	980	985	990	
	Gly Pro Pro Gly Pro Gln Gly Leu	Pro Gly Leu Ala Gly Thr Ala Gly		
	995	1000	1005	
15	Glu Pro Gly Arg Asp Gly Asn	Pro Gly Ser Asp Gly Leu Pro Gly Arg		
	1010	1015	1020	
20	Asp Gly Ser Pro Gly Gly Lys Gly	Asp Arg Gly Glu Asn Gly Ser Pro		
	1025	1030	1035	1040
	Gly Ala Pro Gly Ala Pro Gly His	Pro Gly Pro Pro Gly Pro Val Gly		
25	1045	1050	1055	
	Pro Ala Gly Lys Ser Gly Asp Arg	Gly Glu Ser Gly Pro Ala Gly Pro		
	1060	1065	1070	
30	Ala Gly Ala Pro Gly Pro Ala Gly	Ser Arg Gly Ala Pro Gly Pro Gln		
	1075	1080	1085	
35	Gly Pro Arg Gly Asp Lys Gly Glu Thr	Gly Glu Arg Gly Ala Ala Gly		
	1090	1095	1100	
	Ile Lys Gly His Arg Gly Phe Pro	Gly Asn Pro Gly Ala Pro Gly Ser		
40	1105	1110	1115	1120
	Pro Gly Pro Ala Gly Gln Gln Gly	Ala Ile Gly Ser Pro Gly Pro Ala		
	1125	1130	1135	
45	Gly Pro Arg Gly Pro Val Gly Pro	Ser Gly Pro Pro Gly Lys Asp Gly		
	1140	1145	1150	
50	Thr Ser Gly His Pro Gly Pro Ile	Gly Pro Pro Gly Pro Arg Gly Asn		
	1155	1160	1165	
	Arg Gly Glu Arg Gly Ser Glu Gly	Ser Pro Gly His Pro Gly Gln Pro		
55	1170	1175	1180	

EP 1 439 393 A2

Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Val
5 1185 1190 1195 1200
Gly Ala Ala Ala Ile Ala Gly Ile Gly Gly Glu Lys Ala Gly Gly Phe
1205 1210 1215
10 Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp
1220 1225 1230
15 Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
1235 1240 1245
Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp
20 1250 1255 1260
Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp Val Asp
1265 1270 1275 1280
25 Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Phe Cys Asn Met
1285 1290 1295
30 Glu Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Leu Asn Val Pro Arg
1300 1305 1310
Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys Lys His Val Trp Phe
35 1315 1320 1325
Gly Glu Ser Met Asp Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu
1330 1335 1340
40 Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu
1345 1350 1355 1360
45 Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile
1365 1370 1375
Ala Tyr Met Asp Gln Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu
50 1380 1385 1390
Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe
1395 1400 1405
55 Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp

EP 1 439 393 A2

1410 1415 1420
 Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro
 5
 1425 1430 1435 1440
 Ile Val Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe
 10
 1445 1450 1455
 Gly Val Asp Val Gly Pro Val Cys Phe Leu
 15
 1460 1465
 15
 <210> 104
 20
 <211> 272
 <212> PRT
 25
 <213> Homo sapiens
 <400> 104
 30
 Met Val Leu Leu Thr Ala Val Leu Leu Leu Leu Ala Ala Tyr Ala Gly
 1 5 10 15
 35
 Pro Ala Gln Ser Leu Gly Ser Phe Val His Cys Glu Pro Cys Asp Glu
 20 25 30
 Lys Ala Leu Ser Met Cys Pro Pro Ser Pro Leu Gly Cys Glu Leu Val
 40
 35 40 45
 Lys Glu Pro Gly Cys Gly Cys Cys Met Thr Cys Ala Leu Ala Glu Gly
 50
 50 55 60
 45
 Gln Ser Cys Gly Val Tyr Thr Glu Arg Cys Ala Gln Gly Leu Arg Cys
 65 70 75 80
 50
 Leu Pro Arg Gln Asp Glu Glu Lys Pro Leu His Ala Leu Leu His Gly
 85 90 95
 Arg Gly Val Cys Leu Asn Glu Lys Ser Tyr Arg Glu Gln Val Lys Ile
 55
 100 105 110

EP 1 439 393 A2

Glu Arg Asp Ser Arg Glu His Glu Glu Pro Thr Thr Ser Glu Met Ala
 115 120 125
 5 Glu Glu Thr Tyr Ser Pro Lys Ile Phe Arg Pro Lys His Thr Arg Ile
 130 135 140
 10 Ser Glu Leu Lys Ala Glu Ala Val Lys Lys Asp Arg Arg Lys Lys Leu
 145 150 155 160
 Thr Gln Ser Lys Phe Val Gly Gly Ala Glu Asn Thr Ala His Pro Arg
 15 165 170 175
 Ile Ile Ser Ala Pro Glu Met Arg Gln Glu Ser Glu Gln Gly Pro Cys
 180 185 190
 20 Arg Arg His Met Glu Ala Ser Leu Gln Glu Leu Lys Ala Ser Pro Arg
 195 200 205
 25 Met Val Pro Arg Ala Val Tyr Leu Pro Asn Cys Asp Arg Lys Gly Phe
 210 215 220
 Tyr Lys Arg Lys Gln Cys Lys Pro Ser Arg Gly Arg Lys Arg Gly Ile
 30 225 230 235 240
 Cys Trp Cys Val Asp Lys Tyr Gly Met Lys Leu Pro Gly Met Glu Tyr
 35 245 250 255
 Val Asp Gly Asp Phe Gln Cys His Thr Phe Asp Ser Ser Asn Val Glu
 260 265 270
 40
 45 <210> 105
 <211> 158
 <212> PRT
 50 <213> Homo sapiens
 <400> 105
 55 Met Ala Ser Arg Ser Met Arg Leu Leu Leu Leu Leu Ser Cys Leu Ala

EP 1 439 393 A2

1 5 10 15
 5 Lys Thr Gly Val Leu Gly Asp Ile Ile Met Arg Pro Ser Cys Ala Pro
 20 25 30
 Gly Trp Phe Tyr His Lys Ser Asn Cys Tyr Gly Tyr Phe Arg Lys Leu
 10 35 40 45
 Arg Asn Trp Ser Asp Ala Glu Leu Glu Cys Gln Ser Tyr Gly Asn Gly
 50 55 60
 15 Ala His Leu Ala Ser Ile Leu Ser Leu Lys Glu Ala Ser Thr Ile Ala
 65 70 75 80
 20 Glu Tyr Ile Ser Gly Tyr Gln Arg Ser Gln Pro Ile Trp Ile Gly Leu
 85 90 95
 His Asp Pro Gln Lys Arg Gln Gln Trp Gln Trp Ile Asp Gly Ala Met
 25 100 105 110
 Tyr Leu Tyr Arg Ser Trp Ser Gly Lys Ser Met Gly Gly Asn Lys His
 115 120 125
 30 Cys Ala Glu Met Ser Ser Asn Asn Asn Phe Leu Thr Trp Ser Ser Asn
 130 135 140
 35 Glu Cys Asn Lys Arg Gln His Phe Leu Cys Lys Tyr Arg Pro
 145 150 155
 40
 <210> 106
 45 <211> 175
 <212> PRT
 <213> Homo sapiens
 50
 <400> 106
 55 Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser
 1 5 10 15

EP 1 439 393 A2

Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp
 5 20 25 30
 Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp
 35 40 45
 10 Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys
 50 55 60
 Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu
 15 65 70 75 80
 Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu
 20 85 90 95
 Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu
 100 105 110
 25 Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val Pro Arg Ile
 115 120 125
 Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg
 30 130 135 140
 Tyr Ser Asn Arg Leu Tyr Ala Tyr Glu Pro Ala Asp Thr Ala Leu Leu
 35 145 150 155 160
 Leu Asp Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr Glu Leu
 165 170 175
 40

 45 <210> 107
 <211> 732
 <212> PRT
 50 <213> Homo sapiens

 55 <400> 107
 Met Pro Glu Glu Thr Gln Thr Gln Asp Gln Pro Met Glu Glu Glu Glu

EP 1 439 393 A2

	1	5	10	15												
5	Val	Glu	Thr	Phe	Ala	Phe	Gln	Ala	Glu	Ile	Ala	Gln	Leu	Met	Ser	Leu
		20	25	30												
	Ile	Ile	Asn	Thr	Phe	Tyr	Ser	Asn	Lys	Glu	Ile	Phe	Leu	Arg	Glu	Leu
10		35	40	45												
	Ile	Ser	Asn	Ser	Ser	Asp	Ala	Leu	Asp	Lys	Ile	Arg	Tyr	Glu	Ser	Leu
	50	55	60													
15	Thr	Asp	Pro	Ser	Lys	Leu	Asp	Ser	Gly	Lys	Glu	Leu	His	Ile	Asn	Leu
	65	70	75	80												
20	Ile	Pro	Asn	Lys	Gln	Asp	Arg	Thr	Leu	Thr	Ile	Val	Asp	Thr	Gly	Ile
		85	90	95												
	Gly	Met	Thr	Lys	Ala	Asp	Leu	Ile	Asn	Asn	Leu	Gly	Thr	Ile	Ala	Lys
25		100	105	110												
	Ser	Gly	Thr	Lys	Ala	Phe	Met	Glu	Ala	Leu	Gln	Ala	Gly	Ala	Asp	Ile
		115	120	125												
30	Ser	Met	Ile	Gly	Gln	Phe	Gly	Val	Gly	Phe	Tyr	Ser	Ala	Tyr	Leu	Val
	130	135	140													
35	Ala	Glu	Lys	Val	Thr	Val	Ile	Thr	Lys	His	Asn	Asp	Asp	Glu	Gln	Tyr
	145	150	155	160												
	Ala	Trp	Glu	Ser	Ser	Ala	Gly	Gly	Ser	Phe	Thr	Val	Arg	Thr	Asp	Thr
40		165	170	175												
	Gly	Glu	Pro	Met	Gly	Arg	Gly	Thr	Lys	Val	Ile	Leu	His	Leu	Lys	Glu
		180	185	190												
45	Asp	Gln	Thr	Glu	Tyr	Leu	Glu	Glu	Arg	Arg	Ile	Lys	Glu	Ile	Val	Lys
		195	200	205												
50	Lys	His	Ser	Gln	Phe	Ile	Gly	Tyr	Pro	Ile	Thr	Leu	Phe	Val	Glu	Lys
	210	215	220													
	Glu	Arg	Asp	Lys	Glu	Val	Ser	Asp	Asp	Glu	Ala	Glu	Glu	Lys	Glu	Asp
55	225	230	235	240												

EP 1 439 393 A2

Lys Glu Glu Glu Lys Glu Lys Glu Glu Lys Glu Ser Glu Asp Lys Pro
 245 250 255
 5 Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Lys Lys Asp Gly
 260 265 270
 10 Asp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu
 275 280 285
 Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile
 15 290 295 300
 Thr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp
 20 305 310 315 320
 Glu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu
 325 330 335
 25 Phe Arg Ala Leu Leu Phe Val Pro Arg Arg Ala Pro Phe Asp Leu Phe
 340 345 350
 Glu Asn Arg Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val
 30 355 360 365
 Phe Ile Met Asp Asn Cys Glu Glu Leu Ile Pro Glu Tyr Leu Asn Phe
 35 370 375 380
 Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg
 385 390 395 400
 40 Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu
 405 410 415
 Val Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu
 45 420 425 430
 Asn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly
 50 435 440 445
 Ile His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg
 450 455 460
 55 Tyr Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr

EP 1 439 393 A2

	465		470		475		480									
5	Cys	Thr	Arg	Met	Lys	Glu	Asn	Gln	Lys	His	Ile	Tyr	Tyr	Ile	Thr	Gly
			485						490							495
	Glu	Thr	Lys	Asp	Gln	Val	Ala	Asn	Ser	Ala	Phe	Val	Glu	Arg	Leu	Arg
10			500						505						510	
	Lys	His	Gly	Leu	Glu	Val	Ile	Tyr	Met	Ile	Glu	Pro	Ile	Asp	Glu	Tyr
			515						520						525	
15	Cys	Val	Gln	Gln	Leu	Lys	Glu	Phe	Glu	Gly	Lys	Thr	Leu	Val	Ser	Val
			530						535						540	
20	Thr	Lys	Glu	Gly	Leu	Glu	Leu	Pro	Glu	Asp	Glu	Glu	Glu	Lys	Lys	Lys
			545						550						555	
	Gln	Glu	Glu	Lys	Lys	Thr	Lys	Phe	Glu	Asn	Leu	Cys	Lys	Ile	Met	Lys
25			565						570						575	
	Asp	Ile	Leu	Glu	Lys	Lys	Val	Glu	Lys	Val	Val	Val	Ser	Asn	Arg	Leu
			580						585						590	
30	Val	Thr	Ser	Pro	Cys	Cys	Ile	Val	Thr	Ser	Thr	Tyr	Gly	Trp	Thr	Ala
			595						600						605	
35	Asn	Met	Glu	Arg	Ile	Met	Lys	Ala	Gln	Ala	Leu	Arg	Asp	Asn	Ser	Thr
			610						615						620	
	Met	Gly	Tyr	Met	Ala	Ala	Lys	Lys	His	Leu	Glu	Ile	Asn	Pro	Asp	His
40			625						630						635	
	Ser	Ile	Ile	Glu	Thr	Leu	Arg	Gln	Lys	Ala	Glu	Ala	Asp	Lys	Asn	Asp
			645						650						655	
45	Lys	Ser	Val	Lys	Asp	Leu	Val	Ile	Leu	Leu	Tyr	Glu	Thr	Ala	Leu	Leu
			660						665						670	
50	Ser	Ser	Gly	Phe	Ser	Leu	Glu	Asp	Pro	Gln	Thr	His	Ala	Asn	Arg	Ile
			675						680						685	
	Tyr	Arg	Met	Ile	Lys	Leu	Gly	Leu	Gly	Ile	Asp	Glu	Asp	Asp	Pro	Thr
55			690						695						700	

EP 1 439 393 A2

Ala Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu
5 705 710 715 720
Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp
725 730
10
<210> 108
15 <211> 1361
<212> PRT
20 <213> Homo sapiens
<400> 108
25 Met Gly Ala Ala Gly Arg Gln Asp Phe Leu Phe Lys Ala Met Leu Thr
1 5 10 15
Ile Ser Trp Leu Thr Leu Thr Cys Phe Pro Gly Ala Thr Ser Thr Val
30 20 25 30
Ala Ala Gly Cys Pro Asp Gln Ser Pro Glu Leu Gln Pro Trp Asn Pro
35 35 40 45
Gly His Asp Gln Asp His His Val His Ile Gly Gln Gly Lys Thr Leu
50 55 60
40 Leu Leu Thr Ser Ser Ala Thr Val Tyr Ser Ile His Ile Ser Glu Gly
65 70 75 80
Gly Lys Leu Val Ile Lys Asp His Asp Glu Pro Ile Val Leu Arg Thr
45 85 90 95
Arg His Ile Leu Ile Asp Asn Gly Gly Glu Leu His Ala Gly Ser Ala
50 100 105 110
Leu Cys Pro Phe Gln Gly Asn Phe Thr Ile Ile Leu Tyr Gly Arg Ala
115 120 125
55 Asp Glu Gly Ile Gln Pro Asp Pro Tyr Tyr Gly Leu Lys Tyr Ile Gly

EP 1 439 393 A2

	130	135	140	
5	Val Gly Lys Gly Gly Ala Leu Glu Leu His Gly Gln Lys Lys Leu Ser			
	145	150	155	160
	Trp Thr Phe Leu Asn Lys Thr Leu His Pro Gly Gly Met Ala Glu Gly			
10		165	170	175
	Gly Tyr Phe Phe Glu Arg Ser Trp Gly His Arg Gly Val Ile Val His			
		180	185	190
15	Val Ile Asp Pro Lys Ser Gly Thr Val Ile His Ser Asp Arg Phe Asp			
	195	200	205	
20	Thr Tyr Arg Ser Lys Lys Glu Ser Glu Arg Leu Val Gln Tyr Leu Asn			
	210	215	220	
	Ala Val Pro Asp Gly Arg Ile Leu Ser Val Ala Val Asn Asp Glu Gly			
25	225	230	235	240
	Ser Arg Asn Leu Asp Asp Met Ala Arg Lys Ala Met Thr Lys Leu Gly			
		245	250	255
30	Ser Lys His Phe Leu His Leu Gly Phe Arg His Pro Trp Ser Phe Leu			
	260	265	270	
35	Thr Val Lys Gly Asn Pro Ser Ser Ser Val Glu Asp His Ile Glu Tyr			
	275	280	285	
	His Gly His Arg Gly Ser Ala Ala Ala Arg Val Phe Lys Leu Phe Gln			
40	290	295	300	
	Thr Glu His Gly Glu Tyr Phe Asn Val Ser Leu Ser Ser Glu Trp Val			
45	305	310	315	320
	Gln Asp Val Glu Trp Thr Glu Trp Phe Asp His Asp Lys Val Ser Gln			
		325	330	335
50	Thr Lys Gly Gly Glu Lys Ile Ser Asp Leu Trp Lys Ala His Pro Gly			
	340	345	350	
	Lys Ile Cys Asn Arg Pro Ile Asp Ile Gln Ala Thr Thr Met Asp Gly			
55	355	360	365	

EP 1 439 393 A2

Val Asn Leu Ser Thr Glu Val Val Tyr Lys Lys Gly Gln Asp Tyr Arg
 370 375 380
 5 Phe Ala Cys Tyr Asp Arg Gly Arg Ala Cys Arg Ser Tyr Arg Val Arg
 385 390 395 400
 10 Phe Leu Cys Gly Lys Pro Val Arg Pro Lys Leu Thr Val Thr Ile Asp
 405 410 415
 Thr Asn Val Asn Ser Thr Ile Leu Asn Leu Glu Asp Asn Val Gln Ser
 15 420 425 430
 Trp Lys Pro Gly Asp Thr Leu Val Ile Ala Ser Thr Asp Tyr Ser Met
 20 435 440 445
 Tyr Gln Ala Glu Glu Phe Gln Val Leu Pro Cys Arg Ser Cys Ala Pro
 450 455 460
 25 Asn Gln Val Lys Val Ala Gly Lys Pro Met Tyr Leu His Ile Gly Glu
 465 470 475 480
 Glu Ile Asp Gly Val Asp Met Arg Ala Glu Val Gly Leu Leu Ser Arg
 30 485 490 495
 Asn Ile Ile Val Met Gly Glu Met Glu Asp Lys Cys Tyr Pro Tyr Arg
 35 500 505 510
 Asn His Ile Cys Asn Phe Phe Asp Phe Asp Thr Phe Gly Gly His Ile
 515 520 525
 40 Lys Phe Ala Leu Gly Phe Lys Ala Ala His Leu Glu Gly Thr Glu Leu
 530 535 540
 Lys His Met Gly Gln Gln Leu Val Gly Gln Tyr Pro Ile His Phe His
 45 545 550 555 560
 Leu Ala Gly Asp Val Asp Glu Arg Gly Gly Tyr Asp Pro Pro Thr Tyr
 50 565 570 575
 Ile Arg Asp Leu Ser Ile His His Thr Phe Ser Arg Cys Val Thr Val
 580 585 590
 55 His Gly Ser Asn Gly Leu Leu Ile Lys Asp Val Val Gly Tyr Asn Ser

EP 1 439 393 A2

	595	600	605
5	Leu Gly His Cys Phe Phe Thr Glu Asp Gly Pro Glu Glu Arg Asn Thr		
	610	615	620
	Phe Asp His Cys Leu Gly Leu Leu Val Lys Ser Gly Thr Leu Leu Pro		
10	625	630	635
	Ser Asp Arg Asp Ser Lys Met Cys Lys Met Ile Thr Glu Asp Ser Tyr		640
	645	650	655
15	Pro Gly Tyr Ile Pro Lys Pro Arg Gln Asp Cys Asn Ala Val Ser Thr		
	660	665	670
20	Phe Trp Met Ala Asn Pro Asn Asn Asn Leu Ile Asn Cys Ala Ala Ala		
	675	680	685
	Gly Ser Glu Glu Thr Gly Phe Trp Phe Ile Phe His His Val Pro Thr		
25	690	695	700
	Gly Pro Ser Val Gly Met Tyr Ser Pro Gly Tyr Ser Glu His Ile Pro		
	705	710	715
30	Leu Gly Lys Phe Tyr Asn Asn Arg Ala His Ser Asn Tyr Arg Ala Gly		720
	725	730	735
35	Met Ile Ile Asp Asn Gly Val Lys Thr Thr Glu Ala Ser Ala Lys Asp		
	740	745	750
	Lys Arg Pro Phe Leu Ser Ile Ile Ser Ala Arg Tyr Ser Pro His Gln		
40	755	760	765
	Asp Ala Asp Pro Leu Lys Pro Arg Glu Pro Ala Ile Ile Arg His Phe		
	770	775	780
45	Ile Ala Tyr Lys Asn Gln Asp His Gly Ala Trp Leu Arg Gly Gly Asp		
	785	790	795
	Val Trp Leu Asp Ser Cys Arg Phe Ala Asp Asn Gly Ile Gly Leu Thr		800
50	805	810	815
	Leu Ala Ser Gly Gly Thr Phe Pro Tyr Asp Asp Gly Ser Lys Gln Glu		
55	820	825	830

EP 1 439 393 A2

Ile Lys Asn Ser Leu Phe Val Gly Glu Ser Gly Asn Val Gly Thr Glu
5 835 840 845
Met Met Asp Asn Arg Ile Trp Gly Pro Gly Gly Leu Asp His Ser Gly
 850 855 860
10 Arg Thr Leu Pro Ile Gly Gln Asn Phe Pro Ile Arg Gly Ile Gln Leu
865 870 875 880
Tyr Asp Gly Pro Ile Asn Ile Gln Asn Cys Thr Phe Arg Lys Phe Val
15 885 890 895
Ala Leu Glu Gly Arg His Thr Ser Ala Leu Ala Phe Arg Leu Asn Asn
 900 905 910
20 Ala Trp Gln Ser Cys Pro His Asn Asn Val Thr Gly Ile Ala Phe Glu
 915 920 925
25 Asp Val Pro Ile Thr Ser Arg Val Phe Phe Gly Glu Pro Gly Pro Trp
930 935 940
Phe Asn Gln Leu Asp Met Asp Gly Asp Lys Thr Ser Val Phe His Asp
30 945 950 955 960
Val Asp Gly Ser Val Ser Glu Tyr Pro Gly Ser Tyr Leu Thr Lys Asn
 965 970 975
35 Asp Asn Trp Leu Val Arg His Pro Asp Cys Ile Asn Val Pro Asp Trp
 980 985 990
40 Arg Gly Ala Ile Cys Ser Gly Cys Tyr Ala Gln Met Tyr Ile Gln Ala
 995 1000 1005
Tyr Lys Thr Ser Asn Leu Arg Met Lys Ile Ile Lys Asn Asp Phe Pro
45 1010 1015 1020
Ser His Pro Leu Tyr Leu Glu Gly Ala Leu Thr Arg Ser Thr His Tyr
1025 1030 1035 1040
50 Gln Gln Tyr Gln Pro Val Val Thr Leu Gln Lys Gly Tyr Thr Ile His
 1045 1050 1055
55 Trp Asp Gln Thr Ala Pro Ala Glu Leu Ala Ile Trp Leu Ile Asn Phe

EP 1 439 393 A2

	1060	1065	1070
5	Asn Lys Gly Asp Trp Ile Arg Val Gly Leu Cys Tyr Pro Arg Gly Thr		
	1075	1080	1085
	Thr Phe Ser Ile Leu Ser Asp Val His Asn Arg Leu Leu Lys Gln Thr		
10	1090	1095	1100
	Ser Lys Thr Gly Val Phe Val Arg Thr Leu Gln Met Asp Lys Val Glu		
	1105	1110	1115
15	Gln Ser Tyr Pro Gly Arg Ser His Tyr Tyr Trp Asp Glu Asp Ser Gly		
	1125	1130	1135
	Leu Leu Phe Leu Lys Leu Lys Ala Gln Asn Glu Arg Glu Lys Phe Ala		
20	1140	1145	1150
	Phe Cys Ser Met Lys Gly Cys Glu Arg Ile Lys Ile Lys Ala Leu Ile		
25	1155	1160	1165
	Pro Lys Asn Ala Gly Val Ser Asp Cys Thr Ala Thr Ala Tyr Pro Lys		
	1170	1175	1180
30	Phe Thr Glu Arg Ala Val Val Asp Val Pro Met Pro Lys Lys Leu Phe		
	1185	1190	1195
	Gly Ser Gln Leu Lys Thr Lys Asp His Phe Leu Glu Val Lys Met Glu		
35	1205	1210	1215
	Ser Ser Lys Gln His Phe Phe His Leu Trp Asn Asp Phe Ala Tyr Ile		
40	1220	1225	1230
	Glu Val Asp Gly Lys Lys Tyr Pro Ser Ser Glu Asp Gly Ile Gln Val		
	1235	1240	1245
45	Val Val Ile Asp Gly Asn Gln Gly Arg Val Val Ser His Thr Ser Phe		
	1250	1255	1260
	Arg Asn Ser Ile Leu Gln Gly Ile Pro Trp Gln Leu Phe Asn Tyr Val		
50	1265	1270	1275
	Ala Thr Ile Pro Asp Asn Ser Ile Val Leu Met Ala Ser Lys Gly Arg		
55	1285	1290	1295

EP 1 439 393 A2

Tyr Val Ser Arg Gly Pro Trp Thr Arg Val Leu Glu Lys Leu Gly Ala
 1300 1305 1310
 5 Asp Arg Gly Leu Lys Leu Lys Glu Gln Met Ala Phe Val Gly Phe Lys
 1315 1320 1325
 10 Gly Ser Phe Arg Pro Ile Trp Val Thr Leu Asp Thr Glu Asp His Lys
 1330 1335 1340
 Ala Lys Ile Phe Gln Val Val Pro Ile Pro Val Val Lys Lys Lys Lys
 15 1345 1350 1355 1360
 Leu
 20
 25 <210> 109
 <211> 469
 <212> PRT
 30 <213> Homo sapiens
 35 <400> 109
 Met His Ser Phe Pro Pro Leu Leu Leu Leu Leu Phe Trp Gly Val Val
 1 5 10 15
 40 Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp
 20 25 30
 Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly
 45 35 40 45
 Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu
 50 55 60
 50 Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp
 65 70 75 80
 55 Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp

EP 1 439 393 A2

	85	90	95
5	Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr		
	100	105	110
	His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala		
10	115	120	125
	Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val		
	130	135	140
15	Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met		
	145	150	155
	Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly		
20	165	170	175
	Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly		
25	180	185	190
	Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg		
	195	200	205
30	Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu		
	210	215	220
	Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr		
35	225	230	235
	Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile		
40	245	250	255
	Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro		
	260	265	270
45	Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr		
	275	280	285
	Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg		
50	290	295	300
	Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe		
55	305	310	315
			320

EP 1 439 393 A2

Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp
325 330 335
5 Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln
340 345 350
10 Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe
355 360 365
Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu
15 370 375 380
Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr
385 390 395 400
20 Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala
405 410 415
25 His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys
420 425 430
Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp
30 435 440 445
Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe
450 455 460
35 Asn Cys Arg Lys Asn
465
40
<210> 110
45 <211> 267
<212> PRT
<213> Homo sapiens
50
<400> 110
55 Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu .

EP 1 439 393 A2

	1	5	10	15
5	Ala	Leu	Pro	Leu
	20	25	30	
	Glu	Gln	Ala	Gln
10	35	40	45	
	Thr	Lys	Asn	Ala
15	50	55	60	
	Phe	Phe	Gly	Leu
	65	70	75	80
20	Ile	Met	Gln	Lys
	85	90	95	
	Leu	Phe	Pro	Asn
25	100	105	110	
	Ile	Val	Ser	Tyr
30	115	120	125	
	Val	Ser	Lys	Ala
	130	135	140	
35	Arg	Lys	Val	Val
	145	150	155	160
	Gly	Ala	His	Gly
40	165	170	175	
	Ala	His	Ala	Phe
45	180	185	190	
	Asp	Glu	Asp	Glu
	195	200	205	
50	Leu	Tyr	Ala	Ala
	210	215	220	
	Ser	Ser	Asp	Pro
55	225	230	235	240

EP 1 439 393 A2

Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
245 250 255
5
Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
260 265
10
<210> 111
15
<211> 216
<212> PRT
<213> Homo sapiens
20
<400> 111
25
Met Arg Pro Arg Ser Gly Pro Thr Arg Asn Pro Arg Leu Arg Ala Phe
1 5 10 15
Ala Gly Val Pro Thr Arg Gly Arg Thr Arg Gly Gln Ser Arg Arg Cys
30 20 25 30
Ala Ala Glu Ala Ser Ala Gly Pro Glu Arg Asp Ala Arg Pro Gly Ala
35 35 40 45
Pro Ala Ala Gly Thr Met Gly Ala Ala His Ser Ala Ser Glu Glu Val
50 55 60
40
Arg Glu Leu Glu Gly Lys Thr Gly Phe Ser Ser Asp Gln Ile Glu Gln
65 70 75 80
Leu His Arg Arg Phe Lys Gln Leu Ser Gly Asp Gln Pro Thr Ile Arg
45 85 90 95
Lys Glu Asn Phe Asn Asn Val Pro Asp Leu Glu Leu Asn Pro Ile Arg
100 105 110
50
Ser Lys Ile Val Arg Ala Phe Phe Asp Asn Arg Asn Leu Arg Lys Gly
115 120 125
55
Pro Ser Gly Leu Ala Asp Glu Ile Asn Phe Glu Asp Phe Leu Thr Ile

EP 1 439 393 A2

130 135 140
 5 Met Ser Tyr Phe Arg Pro Ile Asp Thr Thr Met Asp Glu Glu Gln Val
 145 150 155 160
 Glu Leu Ser Arg Lys Glu Lys Leu Arg Phe Leu Phe His Met Tyr Asp
 10 165 170 175
 Ser Asp Ser Asp Gly Arg Ile Thr Leu Glu Glu Tyr Arg Asn Val Lys
 15 180 185 190
 Trp Ser Arg Ser Cys Cys Arg Glu Thr Leu Thr Ser Arg Arg Ser Pro
 195 200 205
 20 Leu Ala Pro Ser Pro Thr Gly Pro
 210 215
 25
 <210> 112
 <211> 422
 30 <212> PRT
 <213> Homo sapiens
 35
 <400> 112
 Met Asn Ser Gly His Ser Phe Ser Gln Thr Pro Ser Ala Ser Phe His
 40 1 5 10 15
 Gly Ala Gly Gly Gly Trp Gly Arg Pro Arg Ser Phe Pro Arg Ala Pro
 20 25 30
 45 Thr Val His Gly Gly Ala Gly Gly Ala Arg Ile Ser Leu Ser Phe Thr
 35 40 45
 Thr Arg Ser Cys Pro Pro Pro Gly Gly Ser Trp Gly Ser Gly Arg Ser
 50 50 55 60
 Ser Pro Leu Leu Gly Gly Asn Gly Lys Ala Thr Met Gln Asn Leu Asn
 55 65 70 75 80

EP 1 439 393 A2

	Asp	Arg	Leu	Ala	Ser	Tyr	Val	Glu	Lys	Val	Arg	Ala	Leu	Glu	Glu	Ala
5								85			90				95	
	Asn	Met	Lys	Leu	Glu	Ser	Arg	Ile	Leu	Lys	Trp	His	Gln	Gln	Arg	Asp
				100						105				110		
10	Pro	Gly	Ser	Lys	Lys	Asp	Tyr	Ser	Gln	Tyr	Glu	Glu	Asn	Ile	Thr	His
				115					120				125			
	Leu	Gln	Glu	Gln	Ile	Val	Asp	Gly	Lys	Met	Thr	Asn	Ala	Gln	Ile	Ile
15				130					135				140			
	Leu	Leu	Ile	Asp	Asn	Ala	Arg	Met	Ala	Val	Asp	Asp	Phe	Asn	Leu	Lys
20		145				150					155				160	
	Tyr	Glu	Asn	Glu	His	Ser	Phe	Lys	Lys	Asp	Leu	Glu	Ile	Glu	Val	Glu
						165				170				175		
25	Gly	Leu	Arg	Arg	Thr	Leu	Asp	Asn	Leu	Thr	Ile	Val	Thr	Thr	Asp	Leu
						180				185				190		
	Glu	Gln	Glu	Val	Glu	Gly	Met	Arg	Lys	Glu	Leu	Ile	Leu	Met	Lys	Lys
30				195					200				205			
	His	His	Glu	Gln	Glu	Met	Glu	Lys	His	His	Val	Pro	Ser	Asp	Phe	Asn
35			210				215					220				
	Val	Asn	Val	Lys	Val	Asp	Thr	Gly	Pro	Arg	Glu	Asp	Leu	Ile	Lys	Val
		225				230				235				240		
40	Leu	Glu	Asp	Met	Arg	Gln	Glu	Tyr	Glu	Leu	Ile	Ile	Lys	Lys	Lys	His
					245					250				255		
	Arg	Asp	Leu	Asp	Thr	Trp	Tyr	Lys	Glu	Gln	Ser	Ala	Ala	Met	Ser	Gln
45				260					265				270			
	Glu	Ala	Ala	Ser	Pro	Ala	Thr	Val	Gln	Ser	Arg	Gln	Gly	Asp	Ile	His
50			275				280					285				
	Glu	Leu	Lys	Arg	Thr	Phe	Gln	Ala	Leu	Glu	Ile	Asp	Leu	Gln	Thr	Gln
			290				295					300				
55	Tyr	Ser	Thr	Lys	Ser	Ala	Leu	Glu	Asn	Met	Leu	Ser	Glu	Thr	Gln	Ser

EP 1 439 393 A2

305 310 315 320
 5 Arg Tyr Ser Cys Lys Leu Gln Asp Met Gln Glu Ile Ile Ser His Tyr
 325 330 335
 Glu Glu Glu Leu Thr Gln Leu Arg His Glu Leu Glu Arg Gln Asn Asn
 10 340 345 350
 Glu Tyr Gln Val Leu Leu Gly Ile Lys Thr His Leu Glu Lys Glu Ile
 355 360 365
 15 Thr Thr Tyr Arg Arg Leu Leu Glu Gly Glu Ser Glu Gly Thr Arg Glu
 370 375 380
 Glu Ser Lys Ser Ser Met Lys Val Phe Ala Thr Pro Lys Ile Lys Ala
 20 385 390 395 400
 Ile Thr Gln Glu Thr Ile Asn Gly Arg Leu Val Leu Cys Gln Val Asn
 25 405 410 415
 Glu Ile Gln Lys His Ala
 420

30

<210> 113

35

<211> 398

<212> PRT

40

<213> Homo sapiens

<400> 113

45

Met Met Leu Lys Gly Ile Thr Arg Leu Ile Ser Arg Ile His Lys Leu

1 5 10 15

Asp Pro Gly Arg Phe Leu His Met Gly Thr Gln Ala Arg Gln Ser Ile

50

20 25 30

Ala Ala His Leu Asp Asn Gln Val Pro Val Glu Ser Pro Arg Ala Ile

55

35 40 45

EP 1 439 393 A2

Ser Arg Thr Asn Glu Asn Asp Pro Ala Lys His Gly Asp Gln His Glu
 5 50 55 60
 Gly Gln His Tyr Asn Ile Ser Pro Gln Asp Leu Glu Thr Val Phe Pro
 65 70 75 80
 10 His Gly Leu Pro Pro Arg Phe Val Met Gln Val Lys Thr Phe Ser Glu
 85 90 95
 Ala Cys Leu Met Val Arg Lys Pro Ala Leu Glu Leu Leu His Tyr Leu
 15 100 105 110
 Lys Asn Thr Ser Phe Ala Tyr Pro Ala Ile Arg Tyr Leu Leu Tyr Gly
 20 115 120 125
 Glu Lys Gly Thr Gly Lys Thr Leu Ser Leu Cys His Val Ile His Phe
 130 135 140
 25 Cys Ala Lys Gln Asp Trp Leu Ile Leu His Ile Pro Asp Ala His Leu
 145 150 155 160
 Trp Val Lys Asn Cys Arg Asp Leu Leu Gln Ser Ser Tyr Asn Lys Gln
 30 165 170 175
 Arg Phe Asp Gln Pro Leu Glu Ala Ser Thr Trp Leu Lys Asn Phe Lys
 180 185 190
 35 Thr Thr Asn Glu Arg Phe Leu Asn Gln Ile Lys Val Gln Glu Lys Tyr
 195 200 205
 40 Val Trp Asn Lys Arg Glu Ser Thr Glu Lys Gly Ser Pro Leu Gly Glu
 210 215 220
 Val Val Glu Gln Gly Ile Thr Arg Val Arg Asn Ala Thr Asp Ala Val
 45 225 230 235 240
 Gly Ile Val Leu Lys Glu Leu Lys Arg Gln Ser Ser Leu Gly Met Phe
 245 250 255
 50 His Leu Leu Val Ala Val Asp Gly Ile Asn Ala Leu Trp Gly Arg Thr
 260 265 270
 55 Thr Leu Lys Arg Glu Asp Lys Ser Pro Ile Ala Pro Glu Glu Leu Ala

EP 1 439 393 A2

275 280 285
 5 Leu Val His Asn Leu Arg Lys Met Met Lys Asn Asp Trp His Gly Gly
 290 295 300
 Ala Ile Val Ser Ala Leu Ser Gln Thr Gly Ser Leu Phe Lys Pro Arg
 10 305 310 315 320
 Lys Ala Tyr Leu Pro Gln Glu Leu Leu Gly Lys Glu Gly Phe Asp Ala
 325 330 335
 15 Leu Asp Pro Phe Ile Pro Ile Leu Val Ser Asn Tyr Asn Pro Lys Glu
 340 345 350
 20 Phe Glu Ser Cys Ile Gln Tyr Tyr Leu Glu Asn Asn Trp Leu Gln His
 355 360 365
 Glu Lys Ala Pro Thr Glu Glu Gly Lys Lys Glu Leu Leu Phe Leu Ser
 25 370 375 380
 Asn Ala Asn Pro Ser Leu Leu Glu Arg His Cys Ala Tyr Leu
 385 390 395
 30

 35 <210> 114
 <211> 75
 <212> PRT
 40 <213> Homo sapiens

 <400> 114
 45 Met Leu Ser His Phe Arg Val Lys Val Lys Gly Phe Ile Leu Ile Ser
 1 5 10 15
 50 Lys Tyr Phe Asp Pro Tyr Asp Leu Val Ser Ser Tyr Pro Lys Tyr Gly
 20 25 30
 Pro His Thr Ser Arg Thr Gly Ile Leu Trp Glu Leu Val Arg Asn Val
 55 35 40 45

EP 1 439 393 A2

Glu Ser Leu Val Leu Arg Phe Ser Lys Ser Glu Ser Ala Phe Ser Ser
 5 50 55 60
 Ala Leu Leu Ala Ile His Met Phe Glu Lys Asp
 65 70 75
 10
 <210> 115
 15 <211> 163
 <212> PRT
 20 <213> Homo sapiens
 <400> 115
 25 Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe Gly
 1 5 10 15
 Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp Asn Gly
 30 20 25 30
 Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly
 35 35 40 45
 Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys
 50 55 60
 40 Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His
 65 70 75 80
 Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys
 45 85 90 95
 Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg
 100 105 110
 50 Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn
 115 120 125
 55 Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys

EP 1 439 393 A2

130 135 140

5 Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp

145 150 155 160

Ser Arg Glu

10

15 <210> 116

<211> 483

<212> PRT

20 <213> Homo sapiens

25 <400> 116

Met Ser Ile Arg Val Thr Gln Lys Ser Tyr Lys Val Ser Thr Ser Gly

1 5 10 15

30 Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro Gly Ser Arg

20 25 30

Ile Ser Ser Ser Ser Phe Ser Arg Val Gly Ser Ser Asn Phe Arg Gly

35 35 40 45

Gly Leu Gly Gly Gly Tyr Gly Gly Ala Ser Gly Met Gly Gly Ile Thr

40 50 55 60

Ala Val Thr Val Asn Gln Ser Leu Leu Ser Pro Leu Val Leu Glu Val

65 70 75 80

45 Asp Pro Asn Ile Gln Ala Val Arg Thr Gln Glu Lys Glu Gln Ile Lys

85 90 95

Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu

50 100 105 110

Glu Gln Gln Asn Lys Met Leu Glu Thr Lys Trp Ser Leu Leu Gln Gln

55 115 120 125

EP 1 439 393 A2

Gln Lys Thr Ala Arg Ser Asn Met Asp Asn Met Phe Glu Ser Tyr Ile
130 135 140
5 Asn Asn Leu Arg Arg Gln Leu Glu Thr Leu Gly Gln Glu Lys Leu Lys
145 150 155 160
10 Leu Glu Ala Glu Leu Gly Asn Met Gln Gly Leu Val Glu Asp Phe Lys
165 170 175
Asn Lys Tyr Glu Asp Glu Ile Asn Lys Arg Thr Glu Met Glu Asn Glu
15 180 185 190
Phe Val Leu Ile Lys Lys Asp Val Asp Glu Ala Tyr Met Asn Lys Val
195 200 205
20 Glu Leu Glu Ser Arg Leu Glu Gly Leu Thr Asp Glu Ile Asn Phe Leu
210 215 220
25 Arg Gln Leu Tyr Glu Glu Glu Ile Arg Glu Leu Gln Ser Gln Ile Ser
225 230 235 240
Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Met
30 245 250 255
Asp Ser Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Asp Ile Ala Asn
260 265 270
35 Arg Ser Arg Ala Glu Ala Glu Ser Met Tyr Gln Ile Lys Tyr Glu Glu
275 280 285
40 Leu Gln Ser Leu Ala Gly Lys His Gly Asp Asp Leu Arg Arg Thr Lys
290 295 300
Thr Glu Ile Ser Glu Met Asn Arg Asn Ile Ser Arg Leu Gln Ala Glu
45 305 310 315 320
Ile Glu Gly Leu Lys Gly Gln Arg Ala Ser Leu Glu Ala Ala Ile Ala
325 330 335
50 Asp Ala Glu Gln Arg Gly Glu Leu Ala Ile Lys Asp Ala Asn Ala Lys
340 345 350
55 Leu Ser Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala

EP 1 439 393 A2

355 360 365
 5 Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Asn Val Lys Leu Ala Leu
 370 375 380
 Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser
 10 385 390 395 400
 Arg Leu Glu Ser Gly Met Gln Asn Met Ser Ile His Thr Lys Thr Thr
 405 410 415
 15 Ser Gly Tyr Ala Gly Gly Leu Ser Ser Ala Tyr Gly Gly Leu Thr Ser
 420 425 430
 20 Pro Gly Leu Ser Tyr Ser Leu Gly Ser Ser Phe Gly Ser Gly Ala Gly
 435 440 445
 Ser Ser Ser Phe Ser Arg Thr Ser Ser Ser Arg Ala Val Val Val Lys
 25 450 455 460
 Lys Ile Glu Thr Arg Asp Gly Lys Leu Val Ser Glu Ser Ser Asp Val
 465 470 475 480
 30 Leu Pro Lys

35

<210> 117

40

<211> 430

<212> PRT

<213> Homo sapiens

45

<400> 117

50 Met Ser Phe Thr Thr Arg Ser Thr Phe Ser Thr Asn Tyr Arg Ser Leu
 1 5 10 15
 Gly Ser Val Gln Ala Pro Ser Tyr Gly Ala Arg Pro Val Ser Ser Ala

55

20

25

30

EP 1 439 393 A2

Ala Ser Val Tyr Ala Gly Ala Gly Gly Ser Gly Ser Arg Ile Ser Val
35 40 45
5 Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala
50 55 60
10 Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu
65 70 75 80
Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
15 85 90 95
Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile
100 105 110
20 Arg Glu His Leu Glu Lys Lys Gly Pro Gln Val Arg Asp Trp Ser His
115 120 125
25 Tyr Phe Lys Ile Ile Glu Asp Leu Arg Ala Gln Ile Phe Ala Asn Thr
130 135 140
Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala
30 145 150 155 160
Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln
165 170 175
35 Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr
180 185 190
40 Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu
195 200 205
Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu
45 210 215 220
Gln Ala Gln Ile Ala Ser Ser Gly Leu Thr Val Glu Val Asp Ala Pro
225 230 235 240
50 Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr
245 250 255
55 Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser

EP 1 439 393 A2

	260	265	270
5	Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu		
	275	280	285
	Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln		
10	290	295	300
	Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu		
	305	310	315
15	Glu Asn Ser Leu Arg Glu Val Glu Ala Arg Tyr Ala Leu Gln Met Glu		
	325	330	335
20	Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr		
	340	345	350
	Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn		
25	355	360	365
	Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu		
	370	375	380
30	Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn		
	385	390	395
	Ser Met Gln Thr Ile Gln Lys Thr Thr Thr Arg Arg Ile Val Asp Gly		
35	405	410	415
	Lys Val Val Ser Glu Thr Asn Asp Thr Lys Val Leu Arg His		
40	420	425	430
45	<210> 118		
	<211> 400		
50	<212> PRT		
	<213> Homo sapiens		
55	<400> 118		

EP 1 439 393 A2

Met Thr Ser Tyr Ser Tyr Arg Gln Ser Ser Ala Thr Ser Ser Phe Gly
1 5 10 15
5 Gly Leu Gly Gly Gly Ser Val Arg Phe Gly Pro Gly Val Ala Phe Arg
20 25 30
10 Ala Pro Ser Ile His Gly Gly Ser Gly Gly Arg Gly Val Ser Val Ser
35 40 45
Ser Ala Arg Phe Val Ser Ser Ser Ser Ser Gly Ala Tyr Gly Gly Gly
15 50 55 60
Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu
65 70 75 80
20 Lys Leu Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95
25 Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile
100 105 110
Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly Pro Ser Arg Asp Tyr Ser
30 115 120 125
His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg Asp Lys Ile Leu Gly Ala
130 135 140
35 Thr Ile Glu Asn Ser Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu
145 150 155 160
40 Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg
165 170 175
Met Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu
45 180 185 190
Leu Thr Leu Ala Arg Thr Asp Leu Glu Met Gln Ile Glu Gly Leu Lys
195 200 205
50 Glu Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Ile Ser Thr
210 215 220
55 Leu Arg Gly Gln Val Gly Gly Gln Val Ser Val Glu Val Asp Ser Ala

EP 1 439 393 A2

	225	230	235	240
5	Pro Gly Thr Asp Leu Ala Lys Ile Leu Ser Asp Met Arg Ser Gln Tyr			
		245	250	255
	Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala Glu Ala Trp Phe Thr			
10		260	265	270
	Ser Arg Thr Glu Glu Leu Asn Arg Glu Val Ala Gly His Thr Glu Gln			
		275	280	285
15	Leu Gln Met Ser Arg Ser Glu Val Thr Asp Leu Arg Arg Thr Leu Gln			
		290	295	300
20	Gly Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ala Leu			
		305	310	315
	Glu Asp Thr Leu Ala Glu Thr Glu Ala Arg Phe Gly Ala Gln Leu Ala			
25		325	330	335
	His Ile Gln Ala Leu Ile Ser Gly Ile Glu Ala Gln Leu Gly Asp Val			
		340	345	350
30	Arg Ala Asp Ser Glu Arg Gln Asn Gln Glu Tyr Gln Arg Leu Met Asp			
		355	360	365
35	Ile Lys Ser Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Ser Leu Leu			
		370	375	380
	Glu Gly Gln Glu Asp His Tyr Asn Asn Leu Ser Ala Ser Lys Val Leu			
40		385	390	395
				400
45	<210> 119			
	<211> 424			
	<212> PRT			
50	<213> Homo sapiens			
55	<400> 119			

EP 1 439 393 A2

Met Asp Phe Ser Arg Arg Ser Phe His Arg Ser Leu Ser Ser Ser Leu
1 5 10 15
5 Gln Ala Pro Val Val Ser Thr Val Gly Met Gln Arg Leu Gly Thr Thr
20 25 30
10 Pro Ser Val Tyr Gly Gly Ala Gly Gly Arg Gly Ile Arg Ile Ser Asn
35 40 45
Ser Arg His Thr Val Asn Tyr Gly Ser Asp Leu Thr Gly Gly Gly Asp
15 50 55 60
Leu Phe Val Gly Asn Glu Lys Met Ala Met Gln Asn Leu Asn Asp Arg
65 70 75 80
20 Leu Ala Ser Tyr Leu Glu Lys Val Arg Thr Leu Glu Gln Ser Asn Ser
85 90 95
25 Lys Leu Glu Val Gln Ile Lys Gln Trp Tyr Glu Thr Asn Ala Pro Arg
100 105 110
Ala Gly Arg Asp Tyr Ser Ala Tyr Tyr Arg Gln Ile Glu Glu Leu Arg
30 115 120 125
Ser Gln Ile Lys Asp Ala Gln Leu Gln Asn Ala Arg Cys Val Leu Gln
130 135 140
35 Ile Asp Asn Ala Lys Leu Ala Ala Glu Asp Phe Arg Leu Lys Tyr Glu
145 150 155 160
40 Thr Glu Arg Gly Ile Arg Leu Thr Val Glu Ala Asp Leu Gln Gly Leu
165 170 175
Asn Lys Val Phe Asp Asp Leu Thr Leu His Lys Thr Asp Leu Glu Ile
45 180 185 190
Gln Ile Glu Glu Leu Asn Lys Asp Leu Ala Leu Leu Lys Lys Glu His
195 200 205
50 Gln Glu Glu Val Asp Gly Leu His Lys His Leu Gly Asn Thr Val Asn
210 215 220
Val Glu Val Asp Ala Ala Pro Gly Leu Asn Leu Gly Val Ile Met Asn
55

EP 1 439 393 A2

225 230 235 240
 5 Glu Met Arg Gln Lys Tyr Glu Val Met Ala Gln Lys Asn Leu Gln Glu
 245 250 255
 Ala Lys Glu Gln Phe Glu Arg Gln Thr Ala Val Leu Gln Gln Gln Val
 10 260 265 270
 Thr Val Asn Thr Glu Glu Leu Lys Gly Thr Glu Val Gln Leu Thr Glu
 275 280 285
 15 Leu Arg Arg Thr Ser Gln Ser Leu Glu Ile Glu Leu Gln Ser His Leu
 290 295 300
 Ser Met Lys Glu Ser Leu Glu His Thr Leu Glu Glu Thr Lys Ala Arg
 20 305 310 315 320
 Tyr Ser Ser Gln Leu Ala Asn Leu Gln Ser Leu Leu Ser Ser Leu Glu
 25 325 330 335
 Ala Gln Leu Met Gln Ile Arg Ser Asn Met Glu Arg Gln Asn Asn Glu
 340 345 350
 30 Tyr His Ile Leu Leu Asp Ile Lys Thr Arg Leu Glu Gln Glu Ile Ala
 355 360 365
 Thr Tyr Arg Arg Leu Leu Glu Gly Glu Asp Val Lys Thr Thr Glu Tyr
 35 370 375 380
 Gln Leu Ser Thr Leu Glu Glu Arg Asp Ile Lys Lys Thr Arg Lys Ile
 40 385 390 395 400
 Lys Thr Val Val Gln Glu Val Val Asp Gly Lys Val Val Ser Ser Glu
 405 410 415
 45 Val Lys Glu Val Glu Glu Asn Ile
 420
 50
 <210> 120
 <211> 1255
 55

EP 1 439 393 A2

<212> PRT

5 <213> Homo sapiens

<400> 120

10 Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
1 5 10 15
15 Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
20 25 30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
25 35 40 45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
50 55 60
25 Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
65 70 75 80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
30 85 90 95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
35 100 105 110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
115 120 125
40 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
130 135 140
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
45 145 150 155 160
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
50 165 170 175
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
180 185 190
55 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro

EP 1 439 393 A2

	195	200	205
5	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	210	215	220
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
10	225	230	235
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	245	250	255
15	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	260	265	270
20	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	275	280	285
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
25	290	295	300
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	305	310	315
30	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	325	330	335
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
35	340	345	350
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
40	355	360	365
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	370	375	380
45	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	385	390	395
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
50	405	410	415
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
55	420	425	430

EP 1 439 393 A2

Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
5 435 440 445
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
450 455 460
10 Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
465 470 475 480
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
15 485 490 495
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
500 505 510
20 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
515 520 525
25 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
530 535 540
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
30 545 550 555 560
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
565 570 575
35 Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
580 585 590
40 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
595 600 605
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
45 610 615 620
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
625 630 635 640
50 Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
645 650 655
55 Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala

EP 1 439 393 A2

	660	665	670
5	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	675	680	685
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
10	690	695	700
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	705	710	715
15	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	725	730	735
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
20	740	745	750
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
25	755	760	765
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	770	775	780
30	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	785	790	795
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
35	805	810	815
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
40	820	825	830
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	835	840	845
45	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	850	855	860
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
50	865	870	875
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
55	885	890	895

EP 1 439 393 A2

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
 900 905 910
 5 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
 915 920 925
 10 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn
 930 935 940
 Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser
 15 945 950 955 960
 Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly
 965 970 975
 20 Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe
 980 985 990
 25 Ser Ile Pro Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His
 995 1000 1005
 Ser Thr Lys Thr Asp Ala Ser Ser Thr His His Ser Ser Val Pro Pro
 30 1010 1015 1020
 Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val
 1025 1030 1035 1040
 35 Ser Phe Phe Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser
 1045 1050 1055
 40 Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp
 1060 1065 1070
 Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly
 45 1075 1080 1085
 Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr
 1090 1095 1100
 50 Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln
 1105 1110 1115 1120
 55 Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile

EP 1 439 393 A2

1125 1130 1135
 5 Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser
 1140 1145 1150
 Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys
 10 1155 1160 1165
 Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys
 1170 1175 1180
 15 Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg
 1185 1190 1195 1200
 Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly
 20 1205 1210 1215
 Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val
 25 1220 1225 1230
 Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val
 1235 1240 1245
 30 Ala Ala Ala Ser Ala Asn Leu
 1250 1255
 35
 <210> 121
 40 <211> 5179
 <212> PRT
 <213> Homo sapiens
 45
 <400> 121
 Met Gly Leu Pro Leu Ala Arg Leu Ala Ala Val Cys Leu Ala Leu Ser
 50 1 5 10 15
 Leu Ala Gly Gly Ser Glu Leu Gln Thr Glu Gly Arg Thr Arg Tyr His
 55 20 25 30

EP 1 439 393 A2

	Gly	Arg	Asn	Val	Cys	Ser	Thr	Trp	Gly	Asn	Phe	His	Tyr	Lys	Thr	Phe
					35				40					45		
5	Asp	Gly	Asp	Val	Phe	Arg	Phe	Pro	Gly	Leu	Cys	Asp	Tyr	Asn	Phe	Ala
				50				55					60			
10	Ser	Asp	Cys	Arg	Gly	Ser	Tyr	Lys	Glu	Phe	Ala	Val	His	Leu	Lys	Arg
		65				70				75					80	
	Gly	Pro	Gly	Gln	Ala	Glu	Ala	Pro	Ala	Gly	Val	Glu	Ser	Ile	Leu	Leu
15					85					90					95	
	Thr	Ile	Lys	Asp	Asp	Thr	Ile	Tyr	Leu	Thr	Arg	His	Leu	Ala	Val	Leu
					100					105					110	
20	Asn	Gly	Ala	Val	Val	Ser	Thr	Pro	His	Tyr	Ser	Pro	Gly	Leu	Leu	Ile
					115					120					125	
25	Glu	Lys	Ser	Asp	Ala	Tyr	Thr	Lys	Val	Tyr	Ser	Arg	Ala	Gly	Leu	Thr
		130						135						140		
	Leu	Met	Trp	Asn	Arg	Glu	Asp	Ala	Leu	Met	Leu	Glu	Leu	Asp	Thr	Lys
30		145				150				155					160	
	Phe	Arg	Asn	His	Thr	Cys	Gly	Leu	Cys	Gly	Asp	Tyr	Asn	Gly	Leu	Gln
					165					170					175	
35	Ser	Tyr	Ser	Glu	Phe	Leu	Ser	Asp	Gly	Val	Leu	Phe	Ser	Pro	Leu	Glu
					180					185					190	
40	Phe	Gly	Asn	Met	Gln	Lys	Ile	Asn	Gln	Pro	Asp	Val	Val	Cys	Glu	Asp
					195					200					205	
	Pro	Glu	Glu	Glu	Val	Ala	Pro	Ala	Ser	Cys	Ser	Glu	His	Arg	Ala	Glu
45					210					215					220	
	Cys	Glu	Arg	Leu	Leu	Thr	Ala	Glu	Ala	Phe	Ala	Asp	Cys	Gln	Asp	Leu
		225					230					235			240	
50	Val	Pro	Leu	Glu	Pro	Tyr	Leu	Arg	Ala	Cys	Gln	Gln	Asp	Arg	Cys	Arg
							245					250			255	
55	Cys	Pro	Gly	Gly	Asp	Thr	Cys	Val	Cys	Ser	Thr	Val	Ala	Glu	Phe	Ser

EP 1 439 393 A2

	260	265	270
5	Arg Gln Cys Ser His Ala Gly Gly Arg Pro Gly Asn Trp Arg Thr Ala		
	275	280	285
	Thr Leu Cys Pro Lys Thr Cys Pro Gly Asn Leu Val Tyr Leu Glu Ser		
10	290	295	300
	Gly Ser Pro Cys Met Asp Thr Cys Ser His Leu Glu Val Ser Ser Leu		
	305	310	315
15	Cys Glu Glu His Arg Met Asp Gly Cys Phe Cys Pro Glu Gly Thr Val		
	325	330	335
20	Tyr Asp Asp Ile Gly Asp Ser Gly Cys Val Pro Val Ser Gln Cys His		
	340	345	350
	Cys Arg Leu His Gly His Leu Tyr Thr Pro Gly Gln Glu Ile Thr Asn		
25	355	360	365
	Asp Cys Glu Gln Cys Val Cys Asn Ala Gly Arg Trp Val Cys Lys Asp		
	370	375	380
30	Leu Pro Cys Pro Gly Thr Cys Ala Leu Glu Gly Gly Ser His Ile Thr		
	385	390	395
	Thr Phe Asp Gly Lys Thr Tyr Thr Phe His Gly Asp Cys Tyr Tyr Val		
35	405	410	415
	Leu Ala Lys Gly Asp His Asn Asp Ser Tyr Ala Leu Leu Gly Glu Leu		
40	420	425	430
	Ala Pro Cys Gly Ser Thr Asp Lys Gln Thr Cys Leu Lys Thr Val Val		
	435	440	445
45	Leu Leu Ala Asp Lys Lys Lys Asn Ala Val Val Phe Lys Ser Asp Gly		
	450	455	460
	Ser Val Leu Leu Asn Gln Leu Gln Val Asn Leu Pro His Val Thr Ala		
50	465	470	475
	Ser Phe Ser Val Phe Arg Pro Ser Ser Tyr His Ile Met Val Ser Met		
55	485	490	495

EP 1 439 393 A2

	Ala	Ile	Gly	Val	Arg	Leu	Gln	Val	Gln	Leu	Ala	Pro	Val	Met	Gln	Leu	
5				500					505						510		
	Phe	Val	Thr	Leu	Asp	Gln	Ala	Ser	Gln	Gly	Gln	Val	Gln	Gly	Leu	Cys	
				515					520						525		
10	Gly	Asn	Phe	Asn	Gly	Leu	Glu	Gly	Asp	Asp	Phe	Lys	Thr	Ala	Ser	Gly	
				530					535						540		
	Leu	Val	Glu	Ala	Thr	Gly	Ala	Gly	Phe	Ala	Asn	Thr	Trp	Lys	Ala	Gln	
15				545					550					555		560	
	Ser	Thr	Cys	His	Asp	Lys	Leu	Asp	Trp	Leu	Asp	Asp	Pro	Cys	Ser	Leu	
						565					570					575	
20	Asn	Ile	Glu	Ser	Ala	Asn	Tyr	Ala	Glu	His	Trp	Cys	Ser	Leu	Leu	Lys	
						580					585					590	
25	Lys	Thr	Glu	Thr	Pro	Phe	Gly	Arg	Cys	His	Ser	Ala	Val	Asp	Pro	Ala	
						595					600					605	
	Glu	Tyr	Tyr	Lys	Arg	Cys	Lys	Tyr	Asp	Thr	Cys	Asn	Cys	Gln	Asn	Asn	
30				610					615					620			
	Glu	Asp	Cys	Leu	Cys	Ala	Ala	Leu	Ser	Ser	Tyr	Ala	Arg	Ala	Cys	Thr	
				625					630					635		640	
35	Ala	Lys	Gly	Val	Met	Leu	Trp	Gly	Trp	Arg	Glu	His	Val	Cys	Asn	Lys	
						645					650					655	
40	Asp	Val	Gly	Ser	Cys	Pro	Asn	Ser	Gln	Val	Phe	Leu	Tyr	Asn	Leu	Thr	
						660					665					670	
	Thr	Cys	Gln	Gln	Thr	Cys	Arg	Ser	Leu	Ser	Glu	Ala	Asp	Ser	His	Cys	
45						675					680					685	
	Leu	Glu	Gly	Phe	Ala	Pro	Val	Asp	Gly	Cys	Gly	Cys	Pro	Asp	His	Thr	
						690					695					700	
50	Phe	Leu	Asp	Glu	Lys	Gly	Arg	Cys	Val	Pro	Leu	Ala	Lys	Cys	Ser	Cys	
						705					710					715	
55	Tyr	His	Arg	Gly	Leu	Tyr	Leu	Glu	Ala	Gly	Asp	Val	Val	Val	Arg	Gln	

EP 1 439 393 A2

	725	730	735
5	Glu Glu Arg Cys Val Cys Arg Asp Gly Arg Leu His Cys Arg Gln Ile		
	740	745	750
	Arg Leu Ile Gly Gln Ser Cys Thr Ala Pro Lys Ile His Met Asp Cys		
10	755	760	765
	Ser Asn Leu Thr Ala Leu Ala Thr Ser Lys Pro Arg Ala Leu Ser Cys		
	770	775	780
15	Gln Thr Leu Ala Ala Gly Tyr Tyr His Thr Glu Cys Val Ser Gly Cys		
	785	790	795 800
	Val Cys Pro Asp Gly Leu Met Asp Asp Gly Arg Gly Gly Cys Val Val		
20	805	810	815
	Glu Lys Glu Cys Pro Cys Val His Asn Asn Asp Leu Tyr Ser Ser Gly		
25	820	825	830
	Ala Lys Ile Lys Val Asp Cys Asn Thr Cys Thr Cys Lys Arg Gly Arg		
	835	840	845
30	Trp Val Cys Thr Gln Ala Val Cys His Gly Thr Cys Ser Ile Tyr Gly		
	850	855	860
	Ser Gly His Tyr Ile Thr Phe Asp Gly Lys Tyr Tyr Asp Phe Asp Gly		
35	865	870	875 880
	His Cys Ser Tyr Val Ala Val Gln Asp Tyr Cys Gly Gln Asn Ser Ser		
40	885	890	895
	Leu Gly Ser Phe Ser Ile Ile Thr Glu Asn Val Pro Cys Gly Thr Thr		
	900	905	910
45	Gly Val Thr Cys Ser Lys Ala Ile Lys Ile Phe Met Gly Arg Thr Glu		
	915	920	925
	Leu Lys Leu Glu Asp Lys His Arg Val Val Ile Gln Arg Asp Glu Gly		
50	930	935	940
	His His Val Ala Tyr Thr Thr Arg Glu Val Gly Gln Tyr Leu Val Val		
55	945	950	955 960

EP 1 439 393 A2

Glu Ser Ser Thr Gly Ile Ile Val Ile Trp Asp Lys Arg Thr Thr Val
 5 965 970 975
 Phe Ile Lys Leu Ala Pro Ser Tyr Lys Gly Thr Val Cys Gly Leu Cys
 980 985 990
 10 Gly Asn Phe Asp His Arg Ser Asn Asn Asp Phe Thr Thr Arg Asp His
 995 1000 1005
 Met Val Val Ser Ser Glu Leu Asp Phe Gly Asn Ser Trp Lys Glu Ala
 15 1010 1015 1020
 Pro Thr Cys Pro Asp Val Ser Thr Asn Pro Glu Pro Cys Ser Leu Asn
 20 1025 1030 1035 1040
 Pro His Arg Arg Ser Trp Ala Glu Lys Gln Cys Ser Ile Leu Lys Ser
 1045 1050 1055
 25 Ser Val Phe Ser Ile Cys His Ser Lys Val Asp Pro Lys Pro Phe Tyr
 1060 1065 1070
 Glu Ala Cys Val His Asp Ser Cys Ser Cys Asp Thr Gly Gly Asp Cys
 30 1075 1080 1085
 Glu Cys Phe Cys Ser Ala Val Ala Ser Tyr Ala Gln Glu Cys Thr Lys
 1090 1095 1100
 35 Glu Gly Ala Cys Val Phe Trp Arg Thr Pro Asp Leu Cys Pro Ile Phe
 1105 1110 1115 1120
 40 Cys Asp Tyr Tyr Asn Pro Pro His Glu Cys Glu Trp His Tyr Glu Pro
 1125 1130 1135
 Cys Gly Asn Arg Ser Phe Glu Thr Cys Arg Thr Ile Asn Gly Ile His
 45 1140 1145 1150
 Ser Asn Ile Ser Val Ser Tyr Leu Glu Gly Cys Tyr Pro Arg Cys Pro
 1155 1160 1165
 50 Lys Asp Arg Pro Ile Tyr Glu Glu Asp Leu Lys Lys Cys Val Thr Ala
 1170 1175 1180
 55 Asp Lys Cys Gly Cys Tyr Val Glu Asp Thr His Tyr Pro Pro Gly Ala

EP 1 439 393 A2

	1185	1190	1195	1200
5	Ser Val Pro Thr Glu Glu Thr Cys Lys Ser Cys Val Cys Thr Asn Ser			
	1205	1210	1215	
	Ser Gln Val Val Cys Arg Pro Glu Glu Gly Lys Ile Leu Asn Gln Thr			
10	1220	1225	1230	
	Gln Asp Gly Ala Phe Cys Tyr Trp Glu Ile Cys Gly Pro Asn Gly Thr			
	1235	1240	1245	
15	Val Glu Lys His Phe Asn Ile Cys Ser Ile Thr Thr Arg Pro Ser Thr			
	1250	1255	1260	
	Leu Thr Thr Phe Thr Thr Ile Thr Leu Pro Thr Thr Pro Thr Ser Phe			
20	1265	1270	1275	1280
	Thr Thr Thr Thr Thr Thr Thr Thr Pro Thr Ser Ser Thr Val Leu Ser			
25	1285	1290	1295	
	Thr Thr Pro Lys Leu Cys Cys Leu Trp Ser Asp Trp Ile Asn Glu Asp			
	1300	1305	1310	
30	His Pro Ser Ser Gly Ser Asp Asp Gly Asp Arg Glu Pro Phe Asp Gly			
	1315	1320	1325	
	Val Cys Gly Ala Pro Glu Asp Ile Glu Cys Arg Ser Val Lys Asp Pro			
35	1330	1335	1340	
	His Leu Ser Leu Glu Gln His Gly Gln Lys Val Gln Cys Asp Val Ser			
40	1345	1350	1355	1360
	Val Gly Phe Ile Cys Lys Asn Glu Asp Gln Phe Gly Asn Gly Pro Phe			
	1365	1370	1375	
45	Gly Leu Cys Tyr Asp Tyr Lys Ile Arg Val Asn Cys Cys Trp Pro Met			
	1380	1385	1390	
	Asp Lys Cys Ile Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro			
50	1395	1400	1405	
	Pro Pro Thr Thr Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro			
55	1410	1415	1420	

EP 1 439 393 A2

Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro
 1425 1430 1435 1440
 5 Pro Ile Thr Thr Thr Thr Thr Pro Leu Pro Thr Thr Thr Pro Ser Pro
 1445 1450 1455
 10 Pro Ile Ser Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro
 1460 1465 1470
 Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr
 15 1475 1480 1485
 Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Met
 1490 1495 1500
 20 Thr Thr Pro Ile Thr Pro Pro Ala Ser Thr Thr Thr Leu Pro Pro Thr
 1505 1510 1515 1520
 25 Thr Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Pro Pro Pro Thr
 1525 1530 1535
 Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser
 30 1540 1545 1550
 Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr
 1555 1560 1565
 35 Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr
 1570 1575 1580
 40 Thr Pro Ser Pro Pro Thr Ile Thr Thr Thr Thr Pro Pro Pro Thr Thr
 1585 1590 1595 1600
 Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr
 45 1605 1610 1615
 Thr Pro Ser Pro Pro Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser Thr
 1620 1625 1630
 50 Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Thr
 1635 1640 1645
 55 Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr

EP 1 439 393 A2

	1650	1655	1660
5	Pro Ser Pro Pro Ile Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr		
	1665	1670	1675 1680
	Pro Ser Ser Pro Ile Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met		
10	1685	1690	1695
	Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Ser Pro Ile Thr Thr Thr		
	1700	1705	1710
15	Thr Thr Pro Ser Ser Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Met		
	1715	1720	1725
20	Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met		
	1730	1735	1740
	Thr Thr Leu Pro Pro Thr Thr Thr Ser Ser Pro Leu Thr Thr Thr Pro		
25	1745	1750	1755 1760
	Leu Pro Pro Ser Ile Thr Pro Pro Thr Phe Ser Pro Phe Ser Thr Thr		
	1765	1770	1775
30	Thr Pro Thr Thr Pro Cys Val Pro Leu Cys Asn Trp Thr Gly Trp Leu		
	1780	1785	1790
	Asp Ser Gly Lys Pro Asn Phe His Lys Pro Gly Gly Asp Thr Glu Leu		
35	1795	1800	1805
	Ile Gly Asp Val Cys Gly Pro Gly Trp Ala Ala Asn Ile Ser Cys Arg		
40	1810	1815	1820
	Ala Thr Met Tyr Pro Asp Val Pro Ile Gly Gln Leu Gly Gln Thr Val		
	1825	1830	1835 1840
45	Val Cys Asp Val Ser Val Gly Leu Ile Cys Lys Asn Glu Asp Gln Lys		
	1845	1850	1855
	Pro Gly Gly Val Ile Pro Met Ala Phe Cys Leu Asn Tyr Glu Ile Asn		
50	1860	1865	1870
	Val Gln Cys Cys Glu Cys Val Thr Gln Pro Thr Thr Met Thr Thr Thr		
55	1875	1880	1885

EP 1 439 393 A2

Thr Thr Glu Asn Pro Thr Pro Pro Thr Thr Thr Pro Ile Thr Thr Thr
 5 1890 1895 1900
 Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr
 1905 1910 1915 1920
 10 ; Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro
 1925 1930 1935
 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr
 15 1940 1945 1950
 Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr
 20) 1955 1960 1965
 Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly
 1970 1975 1980
 25 Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr
 1985 1990 1995 2000
 ; Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile
 30 2005 2010 2015
 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln
 2020 2025 2030
 35 Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr
) 2035 2040 2045
 40 Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr
 2050 2055 2060
 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro
 45 2065 2070 2075 2080
 ; Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr
 2085 2090 2095
 50 Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr
 2100 2105 2110
 55 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr

EP 1 439 393 A2

	2115	2120	2125
5	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr		
	2130	2135	2140
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val		
10	2145	2150	2155
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro		
	2165	2170	2175
15	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr		
	2180	2185	2190
20	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro		
	2195	2200	2205
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr		
25	2210	2215	2220
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
	2225	2230	2235
30	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
	2245	2250	2255
35	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	2260	2265	2270
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
40	2275	2280	2285
	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	2290	2295	2300
45	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
	2305	2310	2315
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
50	2325	2330	2335
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
55	2340	2345	2350

EP 1 439 393 A2

Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr
5 2355 2360 2365
Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile
 2370 2375 2380
10 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln
2385 2390 2395 2400
Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr
15 2405 2410 2415
Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr
 2420 2425 2430
20 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro
 2435 2440 2445
25 Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr
2450 2455 2460
Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr
30 2465 2470 2475 2480
Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr
 2485 2490 2495
35 Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr
 2500 2505 2510
40 Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val
 2515 2520 2525
Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro
45 2530 2535 2540
Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr
2545 2550 2555 2560
50 Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro
 2565 2570 2575
55 Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr

EP 1 439 393 A2

	2580	2585	2590
5	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
	2595	2600	2605
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
10	2610	2615	2620
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	2625	2630	2635
15	2640		
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
	2645	2650	2655
20	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	2660	2665	2670
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
25	2675	2680	2685
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
	2690	2695	2700
30	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
	2705	2710	2715
	2720		
	Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr		
35	2725	2730	2735
	Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile		
40	2740	2745	2750
	Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln		
	2755	2760	2765
45	Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr		
	2770	2775	2780
	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr		
50	2785	2790	2795
	2800		
	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro		
55	2805	2810	2815

EP 1 439 393 A2

Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr
5 2820 2825 2830
Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr
2835 2840 2845
10 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr
2850 2855 2860
Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr
15 2865 2870 2875 2880
Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val
2885 2890 2895
20 Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro
2900 2905 2910
25 Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr
2915 2920 2925
Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro
30 2930 2935 2940
Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr
2945 2950 2955 2960
35 Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr
2965 2970 2975
40 Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro
2980 2985 2990
Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr
45 2995 3000 3005
Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr
3010 3015 3020
50 Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro
3025 3030 3035 3040
55 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr

EP 1 439 393 A2

	3045	3050	3055
5	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
	3060	3065	3070
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
10	3075	3080	3085
	Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr		
	3090	3095	3100
15	Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile		
	3105	3110	3115
	3120		
20	Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln		
	3125	3130	3135
	Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr		
25	3140	3145	3150
	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr		
	3155	3160	3165
30	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro		
	3170	3175	3180
	Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr		
35	3185	3190	3195
	3200		
	Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr		
40	3205	3210	3215
	Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr		
	3220	3225	3230
45	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr		
	3235	3240	3245
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val		
50	3250	3255	3260
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro		
55	3265	3270	3275
	3280		

EP 1 439 393 A2

Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr
5 3285 3290 3295
Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro
3300 3305 3310
10 Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr
3315 3320 3325
Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr
15 3330 3335 3340
Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro
20 3345 3350 3355 3360
Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr
3365 3370 3375
25 Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr
3380 3385 3390
Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro
30 3395 3400 3405
Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr
3410 3415 3420
35 Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr
3425 3430 3435 3440
40 Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly
3445 3450 3455
Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr
45 3460 3465 3470
Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile
3475 3480 3485
50 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln
3490 3495 3500
55 Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr

EP 1 439 393 A2

	3505	3510	3515	3520
5	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr			
		3525	3530	3535
	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro			
10		3540	3545	3550
	Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr			
		3555	3560	3565
15	Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr			
		3570	3575	3580
	Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr			
20		3585	3590	3595
				3600
	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr			
25		3605	3610	3615
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val			
		3620	3625	3630
30	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro			
		3635	3640	3645
	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr			
35		3650	3655	3660
	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro			
40		3665	3670	3675
				3680
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr			
		3685	3690	3695
45	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr			
		3700	3705	3710
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro			
50		3715	3720	3725
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr			
55		3730	3735	3740

EP 1 439 393 A2

Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr
5 3745 3750 3755 3760
Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro
3765 3770 3775
10 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr
3780 3785 3790
Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr
15 3795 3800 3805
Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly
20 3810 3815 3820
Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr
3825 3830 3835 3840
25 Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile
3845 3850 3855
Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln
30 3860 3865 3870
Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr
3875 3880 3885
35 Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr
3890 3895 3900
40 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro
3905 3910 3915 3920
Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr
45 3925 3930 3935
Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr
3940 3945 3950
50 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr
3955 3960 3965
55 Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr

EP 1 439 393 A2

	3970	3975	3980	
5	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val			
	3985	3990	3995	4000
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro			
10		4005	4010	4015
	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr			
		4020	4025	4030
15	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro			
		4035	4040	4045
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr			
20		4050	4055	4060
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr			
25		4065	4070	4075
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro			
		4085	4090	4095
30	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr			
		4100	4105	4110
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr			
35		4115	4120	4125
	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro			
40		4130	4135	4140
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr			
		4145	4150	4155
				4160
45	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr			
		4165	4170	4175
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly			
50		4180	4185	4190
	Thr Gln Thr Gly Pro Pro Thr His Thr Ser Thr Ala Pro Ile Ala Glu			
55		4195	4200	4205

EP 1 439 393 A2

Leu Thr Thr Ser Asn Pro Pro Pro Glu Ser Ser Thr Pro Gln Thr Ser
 5 4210 4215 4220
 Arg Ser Thr Ser Ser Pro Leu Thr Glu Ser Thr Thr Leu Leu Ser Thr
 4225 4230 4235 4240
 10 Leu Pro Pro Ala Ile Glu Met Thr Ser Thr Ala Pro Pro Ser Thr Pro
 4245 4250 4255
 Thr Ala Pro Thr Thr Thr Ser Gly Gly His Thr Leu Ser Pro Pro Pro
 15 4260 4265 4270
 Ser Thr Thr Thr Ser Pro Pro Gly Thr Pro Thr Arg Gly Thr Thr Thr
 20 4275 4280 4285
 Gly Ser Ser Ser Ala Pro Thr Pro Ser Thr Val Gln Thr Thr Thr Thr
 4290 4295 4300
 25 Ser Ala Trp Thr Pro Thr Pro Thr Pro Leu Ser Thr Pro Ser Ile Ile
 4305 4310 4315 4320
 Arg Thr Thr Gly Leu Arg Pro Tyr Pro Ser Ser Val Leu Ile Cys Cys
 30 4325 4330 4335
 Val Leu Asn Asp Thr Tyr Tyr Ala Pro Gly Glu Glu Val Tyr Asn Gly
 4340 4345 4350
 35 Thr Tyr Gly Asp Thr Cys Tyr Phe Val Asn Cys Ser Leu Ser Cys Thr
 4355 4360 4365
 40 Leu Glu Phe Tyr Asn Trp Ser Cys Pro Ser Thr Pro Ser Pro Thr Pro
 4370 4375 4380
 Thr Pro Ser Lys Ser Thr Pro Thr Pro Ser Lys Pro Ser Ser Thr Pro
 45 4385 4390 4395 4400
 Ser Lys Pro Thr Pro Gly Thr Lys Pro Pro Glu Cys Pro Asp Phe Asp
 4405 4410 4415
 50 Pro Pro Arg Gln Glu Asn Glu Thr Trp Trp Leu Cys Asp Cys Phe Met
 4420 4425 4430
 55 Ala Thr Cys Lys Tyr Asn Asn Thr Val Glu Ile Val Lys Val Glu Cys

EP 1 439 393 A2

	4435	4440	4445
5	Glu Pro Pro Pro Met Pro Thr Cys Ser Asn Gly Leu Gln Pro Val Arg		
	4450	4455	4460
	Val Glu Asp Pro Asp Gly Cys Cys Trp His Trp Glu Cys Asp Cys Tyr		
10	4465	4470	4475
	Cys Thr Gly Trp Gly Asp Pro His Tyr Val Thr Phe Asp Gly Leu Tyr		
	4485	4490	4495
15	Tyr Ser Tyr Gln Gly Asn Cys Thr Tyr Val Leu Val Glu Glu Ile Ser		
	4500	4505	4510
20	Pro Ser Val Asp Asn Phe Gly Val Tyr Ile Asp Asn Tyr His Cys Asp		
	4515	4520	4525
	Pro Asn Asp Lys Val Ser Cys Pro Arg Thr Leu Ile Val Arg His Glu		
25	4530	4535	4540
	Thr Gln Glu Val Leu Ile Lys Thr Val His Met Met Pro Met Gln Val		
	4545	4550	4555
30	Gln Val Gln Val Asn Arg Gln Ala Val Ala Leu Pro Tyr Lys Lys Tyr		
	4565	4570	4575
	Gly Leu Glu Val Tyr Gln Ser Gly Ile Asn Tyr Val Val Asp Ile Pro		
35	4580	4585	4590
	Glu Leu Gly Val Leu Val Ser Tyr Asn Gly Leu Ser Phe Ser Val Arg		
40	4595	4600	4605
	Leu Pro Tyr His Arg Phe Gly Asn Asn Thr Lys Gly Gln Cys Gly Thr		
	4610	4615	4620
45	Cys Thr Asn Thr Thr Ser Asp Asp Cys Ile Leu Pro Ser Gly Glu Ile		
	4625	4630	4635
	Val Ser Asn Cys Glu Ala Ala Ala Asp Gln Trp Leu Val Asn Asp Pro		
50	4645	4650	4655
	Ser Lys Pro His Cys Pro His Ser Ser Ser Thr Thr Lys Arg Pro Ala		
55	4660	4665	4670

EP 1 439 393 A2

Val Thr Val Pro Gly Gly Gly Lys Thr Thr Pro His Lys Asp Cys Thr
5 4675 4680 4685
Pro Ser Pro Leu Cys Gln Leu Ile Lys Asp Ser Leu Phe Ala Gln Cys
4690 4695 4700
10 His Ala Leu Val Pro Pro Gln His Tyr Tyr Asp Ala Cys Val Phe Asp
4705 4710 4715 4720
Ser Cys Phe Met Pro Gly Ser Ser Leu Glu Cys Ala Ser Leu Gln Ala
15 4725 4730 4735
Tyr Ala Ala Leu Cys Ala Gln Gln Asn Ile Cys Leu Asp Trp Arg Asn
4740 4745 4750
20 His Thr His Gly Ala Cys Leu Val Glu Cys Pro Ser His Arg Glu Tyr
4755 4760 4765
25 Gln Ala Cys Gly Pro Ala Glu Glu Pro Thr Cys Lys Ser Ser Ser Ser
4770 4775 4780
Gln Gln Asn Asn Thr Val Leu Val Glu Gly Cys Phe Cys Pro Glu Gly
30 4785 4790 4795 4800
Thr Met Asn Tyr Ala Pro Gly Phe Asp Val Cys Val Lys Thr Cys Gly
4805 4810 4815
35 Cys Val Gly Pro Asp Asn Val Pro Arg Glu Phe Gly Glu His Phe Glu
4820 4825 4830
40 Phe Asp Cys Lys Asn Cys Val Cys Leu Glu Gly Gly Ser Gly Ile Ile
4835 4840 4845
Cys Gln Pro Lys Arg Cys Ser Gln Lys Pro Val Thr His Cys Val Glu
45 4850 4855 4860
Asp Gly Thr Tyr Leu Ala Thr Glu Val Asn Pro Ala Asp Thr Cys Cys
4865 4870 4875 4880
50 Asn Ile Thr Val Cys Lys Cys Asn Thr Ser Leu Cys Lys Glu Lys Pro
4885 4890 4895
55 Ser Val Cys Pro Leu Gly Phe Glu Val Lys Ser Lys Met Val Pro Gly

EP 1 439 393 A2

	4900	4905	4910	
5	Arg Cys Cys Pro Phe Tyr Trp Cys Glu Ser Lys Gly Val Cys Val His			
	4915	4920	4925	
	Gly Asn Ala Glu Tyr Gln Pro Gly Ser Pro Val Tyr Ser Ser Lys Cys			
10	4930	4935	4940	
	Gln Asp Cys Val Cys Thr Asp Lys Val Asp Asn Asn Thr Leu Leu Asn			
	4945	4950	4955	4960
15	Val Ile Ala Cys Thr His Val Pro Cys Asn Thr Ser Cys Ser Pro Gly			
	4965	4970	4975	
20	Phe Glu Leu Met Glu Ala Pro Gly Glu Cys Cys Lys Lys Cys Glu Gln			
	4980	4985	4990	
	Thr His Cys Ile Ile Lys Arg Pro Asp Asn Gln His Val Ile Leu Lys			
25	4995	5000	5005	
	Pro Gly Asp Phe Lys Ser Asp Pro Lys Asn Asn Cys Thr Phe Phe Ser			
	5010	5015	5020	
30	Cys Val Lys Ile His Asn Gln Leu Ile Ser Ser Val Ser Asn Ile Thr			
	5025	5030	5035	5040
35	Cys Pro Asn Phe Asp Ala Ser Ile Cys Ile Pro Gly Ser Ile Thr Phe			
	5045	5050	5055	
	Met Pro Asn Gly Cys Cys Lys Thr Cys Thr Pro Arg Asn Glu Thr Arg			
40	5060	5065	5070	
	Val Pro Cys Ser Thr Val Pro Val Thr Thr Glu Val Ser Tyr Ala Gly			
	5075	5080	5085	
45	Cys Thr Lys Thr Val Leu Met Asn His Cys Ser Gly Ser Cys Gly Thr			
	5090	5095	5100	
50	Phe Val Met Tyr Ser Ala Lys Ala Gln Ala Leu Asp His Ser Cys Ser			
	5105	5110	5115	5120
	Cys Cys Lys Glu Glu Lys Thr Ser Gln Arg Glu Val Val Leu Ser Cys			
55	5125	5130	5135	

EP 1 439 393 A2

Pro Asn Gly Gly Ser Leu Thr His Thr Tyr Thr His Ile Glu Ser Cys
5 5140 5145 5150
Gln Cys Gln Asp Thr Val Cys Gly Leu Pro Thr Gly Thr Ser Arg Arg
5155 5160 5165
10 Ala Arg Arg Ser Pro Arg His Leu Gly Ser Gly
5170 5175
15
20
<210> 122
<211> 1217
25 <212> PRT
<213> Homo sapiens
30
<400> 122
Ile Thr Ile Thr Glu Thr Thr Ser His Ser Thr Pro Ser Tyr Thr Thr
1 5 10 15
35 Ser Ile Thr Thr Thr Glu Thr Pro Ser His Ser Thr Pro Ser Tyr Thr
20 25 30
40 Thr Ser Ile Thr Thr Thr Glu Thr Pro Ser His Ser Thr Pro Ser Phe
35 40 45
Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Ser
45 50 55 60
Phe Thr Ser Ser Ile Arg Thr Thr Glu Thr Thr Ser Tyr Ser Thr Pro
65 70 75 80
50 Ser Phe Thr Ser Ser Asn Thr Ile Thr Glu Thr Thr Ser His Ser Thr
85 90 95
55 Pro Ser Tyr Ile Thr Ser Ile Thr Thr Thr Glu Thr Pro Ser Ser Ser

EP 1 439 393 A2

	100	105	110
5	Thr Pro Ser Phe Ser Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His		
	115	120	125
	Ser Thr Pro Gly Phe Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser		
10	130	135	140
	His Ser Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr		
	145	150	155
15	Ser His Asp Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Ser Glu Thr		
	165	170	175
20	Pro Ser His Ser Thr Pro Ser Ser Thr Ser Leu Ile Thr Thr Thr Lys		
	180	185	190
	Thr Thr Ser His Ser Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Thr		
25	195	200	205
	Glu Thr Thr Ser His Ser Ala Arg Ser Phe Thr Ser Ser Ile Thr Thr		
	210	215	220
30	Thr Glu Thr Thr Ser His Asn Thr Arg Ser Phe Thr Ser Ser Ile Thr		
	225	230	235
	Thr Thr Glu Thr Asn Ser His Ser Thr Thr Ser Phe Thr Ser Ser Ile		
35	245	250	255
	Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Ser Phe Ser Ser Ser		
40	260	265	270
	Ile Thr Thr Thr Glu Thr Pro Leu His Ser Thr Pro Gly Leu Thr Ser		
	275	280	285
45	Trp Val Thr Thr Thr Lys Thr Thr Ser His Ile Thr Pro Gly Leu Thr		
	290	295	300
	Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Gly Phe		
50	305	310	315
	Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser Glu Ser Thr Pro Ser		
55	325	330	335

EP 1 439 393 A2

Leu Ser Ser Ser Thr Ile Tyr Ser Thr Val Ser Thr Ser Thr Thr Ala
 5 340 345 350
 Ile Thr Ser His Phe Thr Thr Ser Glu Thr Ala Val Thr Pro Thr Pro
 355 360 365
 10 Val Thr Pro Ser Ser Leu Ser Thr Asp Ile Pro Thr Thr Ser Leu Arg
 370 375 380
 Thr Leu Thr Pro Ser Ser Val Gly Thr Ser Thr Ser Leu Thr Thr Thr
 15 385 390 395 400
 Thr Asp Phe Pro Ser Ile Pro Thr Asp Ile Ser Thr Leu Pro Thr Arg
 405 410 415
 20 Thr His Ile Ile Ser Ser Ser Pro Ser Ile Gln Ser Thr Glu Thr Ser
 420 425 430
 25 Ser Leu Val Gly Thr Thr Ser Pro Thr Met Ser Thr Val Arg Met Thr
 435 440 445
 Leu Arg Ile Thr Glu Asn Thr Pro Ile Ser Ser Phe Ser Thr Ser Ile
 30 450 455 460
 Val Val Ile Pro Glu Thr Pro Thr Gln Thr Pro Pro Val Leu Thr Ser
 465 470 475 480
 35 Ala Thr Gly Thr Gln Thr Ser Pro Ala Pro Thr Thr Val Thr Phe Gly
 485 490 495
 40 Ser Thr Asp Ser Ser Thr Ser Thr Leu His Thr Leu Thr Pro Ser Thr
 500 505 510
 Ala Leu Ser Thr Ile Val Ser Thr Ser Gln Val Pro Ile Pro Ser Thr
 45 515 520 525
 His Ser Ser Thr Leu Gln Thr Thr Pro Ser Thr Pro Ser Leu Gln Thr
 530 535 540
 50 Ser Leu Thr Ser Thr Ser Glu Phe Thr Thr Glu Ser Phe Thr Arg Gly
 545 550 555 560
 55 Ser Thr Ser Thr Asn Ala Ile Leu Thr Ser Phe Ser Thr Ile Ile Trp

EP 1 439 393 A2

	565	570	575
5	Ser Ser Thr Pro Thr Ile Ile Met Ser Ser Ser Pro Ser Ser Ala Ser		
	580	585	590
	Ile Thr Pro Val Phe Ser Thr Thr Ile His Ser Val Pro Ser Ser Pro		
10	595	600	605
	Tyr Ile Phe Ser Thr Glu Asn Val Gly Ser Ala Ser Ile Thr Gly Phe		
	610	615	620
15	Pro Ser Leu Ser Ser Ser Ala Thr Thr Ser Thr Ser Ser Thr Ser Ser		
	625	630	635
	Ser Leu Thr Thr Ala Leu Thr Glu Ile Thr Pro Phe Ser Tyr Ile Ser		
20	645	650	655
	Leu Pro Ser Thr Thr Pro Cys Pro Gly Thr Ile Thr Ile Thr Ile Val		
25	660	665	670
	Pro Ala Ser Pro Thr Asp Pro Cys Val Glu Met Asp Pro Ser Thr Glu		
	675	680	685
30	Ala Thr Ser Pro Pro Thr Thr Pro Leu Thr Val Phe Pro Phe Thr Thr		
	690	695	700
	Glu Met Val Thr Cys Pro Thr Ser Ile Ser Ile Gln Thr Thr Leu Thr		
35	705	710	715
	Thr Tyr Met Asp Thr Ser Ser Met Met Pro Glu Ser Glu Ser Ser Ile		
40	725	730	735
	Ser Pro Asn Ala Ser Ser Ser Thr Gly Thr Gly Thr Val Pro Thr Asn		
	740	745	750
45	Thr Val Phe Thr Ser Thr Arg Leu Pro Thr Ser Glu Thr Trp Leu Ser		
	755	760	765
	Asn Ser Ser Val Ile Pro Leu Pro Leu Pro Gly Val Ser Thr Ile Pro		
50	770	775	780
	Leu Thr Met Lys Pro Ser Ser Ser Leu Pro Thr Ile Leu Arg Thr Ser		
55	785	790	795
			800

EP 1 439 393 A2

Ser Lys Ser Thr His Pro Ser Pro Pro Thr Thr Arg Thr Ser Glu Thr
 5 805 810 815
 Pro Val Ala Thr Thr Gln Thr Pro Thr Thr Leu Thr Ser Arg Arg Thr
 820 825 830
 10 Thr Arg Ile Thr Ser Gln Met Thr Thr Gln Ser Thr Leu Thr Thr Thr
 835 840 845
 Ala Gly Thr Cys Asp Asn Gly Gly Thr Trp Glu Gln Gly Gln Cys Ala
 15 850 855 860
 Cys Leu Pro Gly Phe Ser Gly Asp Arg Cys Gln Leu Gln Thr Arg Cys
 20 865 870 875 880
 Gln Asn Gly Gly Gln Trp Asp Gly Leu Lys Cys Gln Cys Pro Ser Thr
 885 890 895
 25 Phe Tyr Gly Ser Ser Cys Glu Phe Ala Val Glu Gln Val Asp Leu Asp
 900 905 910
 Val Val Glu Thr Glu Val Gly Met Glu Val Ser Val Asp Gln Gln Phe
 30 915 920 925
 Ser Pro Asp Leu Asn Asp Asn Thr Ser Gln Ala Tyr Arg Asp Phe Asn
 35 930 935 940
 Lys Thr Phe Trp Asn Gln Met Gln Lys Ile Phe Ala Asp Met Gln Gly
 945 950 955 960
 40 Phe Thr Phe Lys Gly Val Glu Ile Leu Ser Leu Arg Asn Gly Ser Ile
 965 970 975
 Val Val Asp Tyr Leu Val Leu Leu Glu Met Pro Phe Ser Pro Gln Leu
 45 980 985 990
 Glu Ser Glu Tyr Glu Gln Val Lys Thr Thr Leu Lys Glu Gly Leu Gln
 50 995 1000 1005
 Asn Ala Ser Gln Asp Val Asn Ser Cys Gln Asp Ser Gln Thr Leu Cys
 1010 1015 1020
 55 Phe Lys Pro Asp Ser Ile Lys Val Asn Asn Asn Ser Lys Thr Glu Leu

EP 1 439 393 A2

1025 1030 1035 1040
 5 Thr Pro Ala Ala Ile Cys Arg Arg Ala Ala Pro Thr Gly Tyr Glu Glu
 1045 1050 1055
 Phe Tyr Phe Pro Leu Val Glu Ala Thr Arg Leu Arg Cys Val Thr Lys
 10 1060 1065 1070
 Cys Thr Ser Gly Val Asp Asn Ala Ile Asp Cys His Gln Gly Gln Cys
 1075 1080 1085
 15 Val Leu Glu Thr Ser Gly Pro Thr Cys Arg Cys Tyr Ser Thr Asp Thr
 1090 1095 1100
 20 His Trp Phe Ser Gly Pro Arg Cys Glu Val Ala Val His Trp Arg Ala
 1105 1110 1115 1120
 Leu Val Gly Gly Leu Thr Ala Gly Ala Ala Leu Leu Val Leu Leu Leu
 25 1125 1130 1135
 Leu Ala Leu Gly Val Arg Ala Val Arg Ser Gly Trp Trp Gly Gly Gln
 1140 1145 1150
 30 Arg Arg Gly Arg Ser Trp Asp Gln Asp Arg Lys Trp Phe Glu Thr Trp
 1155 1160 1165
 35 Asp Glu Glu Val Val Gly Thr Phe Ser Asn Trp Gly Phe Glu Asp Asp
 1170 1175 1180
 Gly Thr Asp Lys Asp Thr Asn Phe Tyr Val Ala Leu Glu Asn Val Asp
 40 1185 1190 1195 1200
 Thr Thr Met Lys Val His Ile Lys Arg Pro Glu Met Thr Ser Ser Ser
 1205 1210 1215
 45 Val

<210> 123

<211> 1373

<212> PRT

<213> Homo sapiens

<400> 123

5
 10 Met Ser Val Gly Arg Arg Lys Leu Ala Leu Leu Trp Ala Leu Ala Leu
 1 5 10 15
 15 Ala Leu Ala Cys Thr Arg His Thr Gly His Ala Gln Asp Gly Ser Ser
 20 25 30
 25 Glu Ser Ser Tyr Lys His His Pro Ala Leu Ser Pro Ile Ala Arg Gly
 35 40 45
 30 Pro Ile Gly Val Pro Leu Arg Gly Ala Thr Val Phe Pro Ser Leu Arg
 50 55 60
 35 Thr Ile Pro Val Val Arg Ala Ser Asn Pro Ala His Asn Gly Arg Val
 65 70 75 80
 40 Cys Ser Thr Trp Gly Ser Phe His Tyr Lys Thr Phe Asp Gly Asp Val
 85 90 95
 45 Phe Arg Phe Pro Gly Leu Cys Asn Tyr Val Phe Ser Glu His Cys Gly
 100 105 110
 50 Ala Ala Tyr Glu Asp Phe Asn Ile Pro Ala Thr Pro Gln Pro Gly Val
 115 120 125
 55 Ser Gly Pro His Ala Glu Gln Gly Pro His Glu Gly Gly Trp Arg Gly
 130 135 140
 60 His Pro Ala Asp Gln Gly Leu Arg Pro Gly Gln Arg Pro Pro Gly Pro
 145 150 155 160
 65 Ala Ala Leu Gln Pro Val Trp Gly Pro His Ser Ala Arg Ala Ala Ala
 165 170 175
 70 Thr Pro Arg Trp Lys Pro Gly Trp Ala Leu Ser Ser Cys Gly Thr Thr
 180 185 190
 75 Met Thr Ala Cys Cys Trp Lys Leu Asp Thr Lys Tyr Ala Asn Lys Asn

EP 1 439 393 A2

	195	200	205	
5	Leu Trp Ala Leu Trp Gly Leu Gln Arg Asp Ala Arg Gly Gln Arg Ala			
	210	215	220	
	Pro Leu Pro Gln His Gln Ala Asp Thr His Gly Ile Arg Glu Pro Ala			
10	225	230	235	240
	Glu Arg Trp Thr Asn Pro Arg Ser Ser Val Arg Thr Leu Ser Leu Asn			
	245	250	255	
15	Pro Arg Arg Thr Ala Pro Leu Ala Leu Ala Ser Cys Glu Glu Leu Leu			
	260	265	270	
20	His Gly Gln Leu Phe Ser Gly Cys Val Ala Leu Val Asp Val Gly Ser			
	275	280	285	
	Tyr Leu Glu Ala Cys Arg Gln Asp Leu Cys Phe Cys Glu Asp Thr Asp			
25	290	295	300	
	Leu Leu Ser Cys Val Cys His Thr Leu Ala Glu Tyr Ser Arg Gln Cys			
	305	310	315	320
30	Thr His Ala Gly Gly Leu Pro Gln Asp Trp Arg Gly Pro Asp Phe Cys			
	325	330	335	
35	Pro Gln Lys Cys Pro Asn Asn Met Gln Tyr His Glu Cys Arg Ser Pro			
	340	345	350	
	Cys Ala Asp Thr Cys Ser Asn Gln Glu His Ser Arg Ala Cys Glu Asp			
40	355	360	365	
	His Cys Val Ala Gly Cys Phe Cys Pro Glu Gly Thr Val Leu Asp Asp			
	370	375	380	
45	Ile Gly Gln Thr Gly Cys Val Pro Val Ser Lys Cys Ala Cys Val Tyr			
	385	390	395	400
	Asn Gly Ala Ala Tyr Ala Pro Gly Ala Thr Tyr Ser Thr Asp Cys Thr			
50	405	410	415	
	Asn Cys Thr Cys Ser Gly Gly Arg Trp Ser Cys Gln Glu Val Pro Cys			
55	420	425	430	

EP 1 439 393 A2

Pro Gly Thr Cys Ser Val Leu Gly Gly Ala His Phe Ser Thr Phe Asp
5 435 440 445
Gly Lys Gln Tyr Thr Val His Gly Asp Cys Ser Tyr Val Leu Thr Lys
450 455 460
10 Pro Cys Asp Ser Ser Ala Phe Thr Val Leu Ala Glu Leu Arg Arg Cys
465 470 475 480
Gly Leu Thr Asp Ser Glu Thr Cys Leu Lys Ser Val Thr Leu Ser Leu
15 485 490 495
Asp Gly Ala Gln Thr Val Val Val Ile Lys Ala Ser Gly Glu Val Phe
20 500 505 510
Leu Asn Gln Ile Tyr Thr Gln Leu Pro Ile Ser Ala Ala Asn Val Thr
515 520 525
25 Ile Phe Arg Pro Ser Thr Phe Phe Ile Ile Ala Gln Thr Ser Leu Gly
530 535 540
Leu Gln Leu Asn Leu Gln Leu Val Pro Thr Met Gln Leu Phe Met Gln
30 545 550 555 560
Leu Ala Pro Lys Leu Arg Gly Gln Thr Cys Gly Leu Cys Gly Asn Phe
35 565 570 575
Asn Ser Ile Gln Ala Asp Asp Phe Arg Thr Leu Ser Gly Val Val Glu
580 585 590
40 Ala Thr Ala Ala Ala Phe Phe Asn Thr Phe Lys Thr Gln Ala Ala Cys
595 600 605
Pro Asn Ile Arg Asn Ser Phe Glu Asp Pro Cys Ser Leu Ser Val Glu
45 610 615 620
Asn Glu Lys Tyr Ala Gln His Trp Cys Ser Gln Leu Thr Asp Ala Asp
50 625 630 635 640
Gly Pro Phe Gly Arg Cys His Ala Ala Val Lys Pro Gly Thr Tyr Tyr
645 650 655
55 Ser Asn Cys Met Phe Asp Thr Cys Asn Cys Glu Arg Ser Glu Asp Cys

EP 1 439 393 A2

	660	665	670
5	Leu Cys Ala Ala Leu Ser Ser Tyr Val His Ala Cys Ala Ala Lys Gly		
	675	680	685
	Val Gln Leu Gly Gly Trp Arg Asp Gly Val Cys Thr Lys Pro Met Thr		
10	690	695	700
	Thr Cys Pro Lys Ser Met Thr Tyr His Tyr His Val Ser Thr Cys Gln		
	705	710	715
15	Pro Thr Cys Arg Ser Leu Ser Glu Gly Asp Ile Thr Cys Ser Val Gly		
	725	730	735
20	Phe Ile Pro Val Asp Gly Cys Ile Cys Pro Lys Gly Thr Phe Leu Asp		
	740	745	750
	Asp Thr Gly Lys Cys Val Gln Ala Ser Asn Cys Pro Cys Tyr His Arg		
25	755	760	765
	Gly Ser Met Ile Pro Asn Gly Glu Ser Val His Asp Ser Gly Ala Ile		
	770	775	780
30	Cys Thr Cys Thr His Gly Lys Leu Ser Cys Ile Gly Gly Gln Ala Pro		
	785	790	795
	Ala Pro Val Cys Ala Ala Pro Met Val Phe Phe Asp Cys Arg Asn Ala		
35	805	810	815
	Thr Pro Gly Asp Thr Gly Ala Gly Cys Gln Lys Ser Cys His Thr Leu		
40	820	825	830
	Asp Met Thr Cys Tyr Ser Pro Gln Cys Val Pro Gly Cys Val Cys Pro		
	835	840	845
45	Asp Gly Leu Val Ala Asp Gly Glu Gly Gly Cys Ile Thr Ala Glu Asp		
	850	855	860
	Cys Pro Cys Val His Asn Glu Ala Ser Tyr Arg Ala Gly Gln Thr Ile		
50	865	870	875
	Arg Val Gly Cys Asn Thr Cys Thr Cys Asp Ser Arg Met Trp Arg Cys		
55	885	890	895

Thr Asp Asp Pro Cys Leu Ala Thr Cys Ala Val Tyr Gly Asp Gly His
 5 900 905 910
 Tyr Leu Thr Phe Asp Gly Gln Ser Tyr Ser Phe Asn Glu Glu Thr Ala
 915 920 925
 10 Ser Thr Arg Trp Cys Arg Thr Ala Val Ala Gly Lys Thr Ala Pro Arg
 930 935 940
 Thr Pro Phe Val Leu Ser Pro Arg Thr Ser Pro Ala Ala Pro Gln Gly
 15 945 950 955 960
 Pro Pro Ala Pro Arg Pro Ser Arg Phe Ser Trp Gly Asn Phe Glu Leu
 20 965 970 975
 Lys Leu Ser His Gly Lys Val Glu Val Ile Gly Thr Asp Glu Ser Gln
 980 985 990
 25 Glu Val Pro Tyr Thr Ile Arg Gln Met Gly Ile Tyr Leu Val Val Asp
 995 1000 1005
 Thr Asp Ile Gly Leu Val Leu Leu Trp Asp Lys Lys Thr Ser Ile Phe
 30 1010 1015 1020
 Ile Asn Leu Ser Pro Glu Phe Lys Gly Arg Val Cys Gly Leu Cys Gly
 35 1025 1030 1035 1040
 Asn Phe Asp Asp Ile Ala Val Asn Asp Phe Ala Thr Arg Ser Arg Ser
 1045 1050 1055
 40 Val Val Gly Asp Val Leu Glu Phe Gly Asn Ser Trp Lys Leu Ser Pro
 1060 1065 1070
 Ser Cys Pro Asp Ala Leu Ala Pro Lys Asp Pro Cys Thr Ala Asn Pro
 45 1075 1080 1085
 Phe Arg Lys Ser Trp Ala Gln Lys Gln Cys Ser Ile Leu His Gly Pro
 50 1090 1095 1100
 Thr Phe Ala Ala Cys His Ala His Val Glu Pro Ala Arg Tyr Tyr Glu
 1105 1110 1115 1120
 55 Ala Cys Val Asn Asp Ala Cys Ala Cys Asp Ser Gly Gly Asp Cys Glu

EP 1 439 393 A2

	1125	1130	1135
5	Cys Phe Cys Thr Ala Val Ala Arg Tyr Ala Gln Ala Cys His Glu Val		
	1140	1145	1150
	Gly Thr Cys Val Cys Leu Arg Thr Pro Ser Ile Cys Pro Leu Phe Cys		
10	1155	1160	1165
	Asp Tyr Tyr Asn Pro Glu Gly Gln Cys Glu Trp His Tyr Gln Pro Cys		
	1170	1175	1180
15	Gly Val Pro Cys Leu Arg Thr Cys Arg Asn Pro Arg Gly Asp Cys Leu		
	1185	1190	1195
	1200		
20	Arg Asp Val Arg Gly Leu Glu Gly Cys Tyr Pro Lys Cys Pro Pro Glu		
	1205	1210	1215
	Ala Pro Ile Phe Asp Glu Asp Lys Met Gln Cys Val Ala Thr Cys Pro		
25	1220	1225	1230
	Thr Pro Pro Leu Pro Pro Arg Cys His Val His Gly Lys Ser Tyr Arg		
	1235	1240	1245
30	Pro Gly Ala Val Val Pro Ser Asp Lys Asn Cys Gln Ser Cys Leu Cys		
	1250	1255	1260
	Thr Glu Arg Gly Val Glu Cys Thr Tyr Lys Ala Glu Ala Cys Val Cys		
35	1265	1270	1275
	1280		
	Thr Tyr Asn Gly Gln Arg Phe His Pro Gly Asp Val Ile Tyr His Thr		
40	1285	1290	1295
	Thr Asp Gly Thr Gly Gly Cys Ile Ser Ala Arg Cys Gly Ala Asn Gly		
	1300	1305	1310
45	Thr Ile Glu Arg Arg Val Tyr Pro Cys Ser Pro Thr Thr Pro Val Pro		
	1315	1320	1325
	Pro Thr Thr Phe Ser Phe Ser Thr Pro Pro Leu Val Val Ser Ser Thr		
50	1330	1335	1340
	His Thr Pro Ser Asn Gly Pro Ser Ser Ala His Thr Gly Pro Pro Ser		
55	1345	1350	1355
	1360		

EP 1 439 393 A2

Ser Ala Trp Pro Thr Thr Ala Gly Thr Ser Pro Arg Thr
5 1365 1370

10 <210> 124
<211> 165
<212> PRT
15 <213> Homo sapiens

20 <400> 124
Met Glu Met Phe Gln Gly Leu Leu Leu Leu Leu Leu Ser Met Gly
1 5 10 15
25 Gly Thr Trp Ala Ser Lys Glu Pro Leu Arg Pro Arg Cys Arg Pro Ile
20 25 30
Asn Ala Thr Leu Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr
30 35 40 45
Val Asn Thr Thr Ile Cys Ala Gly Tyr Cys Pro Thr Met Thr Arg Val
50 55 60
35 Leu Gln Gly Val Leu Pro Ala Leu Pro Gln Val Val Cys Asn Tyr Arg
65 70 75 80
40 Asp Val Arg Phe Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val
85 90 95
Asn Pro Val Val Ser Tyr Ala Val Ala Leu Ser Cys Gln Cys Ala Leu
45 100 105 110
Cys Arg Arg Ser Thr Thr Asp Cys Gly Gly Pro Lys Asp His Pro Leu
115 120 125
50 Thr Cys Asp Asp Pro Arg Phe Gln Asp Ser Ser Ser Ser Lys Ala Pro
130 135 140
55 Pro Pro Ser Leu Pro Ser Pro Ser Arg Leu Pro Gly Pro Ser Asp Thr

```

145                               150                               155                               160
5   Pro Ile Leu Pro Gln
                                     165
10
    <210> 125
    <211> 1210
15   <212> PRT
    <213> Homo sapiens
20
    <400> 125
Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
25   1               5               10               15
Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln
                20               25               30
30   Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe
                35               40               45
35   Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
                50               55               60
Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys
40   65               70               75               80
Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
                85               90               95
45   Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
                100              105              110
50   Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
                115              120              125
Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
55   130              135              140

```

EP 1 439 393 A2

His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
 5 145 150 155 160
 Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
 165 170 175
 10 Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro
 180 185 190
 Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln
 15 195 200 205
 Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
 20 210 215 220
 Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
 225 230 235 240
 25 Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
 245 250 255
 Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
 30 260 265 270
 Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly
 275 280 285
 35 Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His
 290 295 300
 40 Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu
 305 310 315 320
 Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val
 45 325 330 335
 Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn
 340 345 350
 50 Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp
 355 360 365
 55 Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr

EP 1 439 393 A2

	370	375	380													
5	Pro	Pro	Leu	Asp	Pro	Gln	Glu	Leu	Asp	Ile	Leu	Lys	Thr	Val	Lys	Glu
	385		390		395		400									
	Ile	Thr	Gly	Phe	Leu	Leu	Ile	Gln	Ala	Trp	Pro	Glu	Asn	Arg	Thr	Asp
10		405				410			415							
	Leu	His	Ala	Phe	Glu	Asn	Leu	Glu	Ile	Ile	Arg	Gly	Arg	Thr	Lys	Gln
		420				425			430							
15	His	Gly	Gln	Phe	Ser	Leu	Ala	Val	Val	Ser	Leu	Asn	Ile	Thr	Ser	Leu
		435				440			445							
20	Gly	Leu	Arg	Ser	Leu	Lys	Glu	Ile	Ser	Asp	Gly	Asp	Val	Ile	Ile	Ser
		450				455			460							
	Gly	Asn	Lys	Asn	Leu	Cys	Tyr	Ala	Asn	Thr	Ile	Asn	Trp	Lys	Lys	Leu
25		465				470			475					480		
	Phe	Gly	Thr	Ser	Gly	Gln	Lys	Thr	Lys	Ile	Ile	Ser	Asn	Arg	Gly	Glu
			485						490					495		
30	Asn	Ser	Cys	Lys	Ala	Thr	Gly	Gln	Val	Cys	His	Ala	Leu	Cys	Ser	Pro
		500							505					510		
35	Glu	Gly	Cys	Trp	Gly	Pro	Glu	Pro	Arg	Asp	Cys	Val	Ser	Cys	Arg	Asn
		515							520					525		
	Val	Ser	Arg	Gly	Arg	Glu	Cys	Val	Asp	Lys	Cys	Lys	Leu	Leu	Glu	Gly
40		530							535					540		
	Glu	Pro	Arg	Glu	Phe	Val	Glu	Asn	Ser	Glu	Cys	Ile	Gln	Cys	His	Pro
		545							550					555		560
45	Glu	Cys	Leu	Pro	Gln	Ala	Met	Asn	Ile	Thr	Cys	Thr	Gly	Arg	Gly	Pro
			565							570					575	
	Asp	Asn	Cys	Ile	Gln	Cys	Ala	His	Tyr	Ile	Asp	Gly	Pro	His	Cys	Val
50			580							585					590	
	Lys	Thr	Cys	Pro	Ala	Gly	Val	Met	Gly	Glu	Asn	Asn	Thr	Leu	Val	Trp
55			595							600					605	

EP 1 439 393 A2

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
 5 610 615 620
 Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
 625 630 635 640
 10 Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
 645 650 655
 Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
 15 660 665 670
 Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
 20 675 680 685
 Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
 690 695 700
 25 Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
 705 710 715 720
 Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
 30 725 730 735
 Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
 740 745 750
 35 Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
 755 760 765
 40 Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
 770 775 780
 Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp
 45 785 790 795 800
 Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
 805 810 815
 50 Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg
 820 825 830
 55 Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro

EP 1 439 393 A2

	835	840	845	
5	Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala			
	850	855	860	
	Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp			
10	865	870	875	880
	Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp			
	885	890	895	
15	Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser			
	900	905	910	
20	Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu			
	915	920	925	
	Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr			
25	930	935	940	
	Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys			
	945	950	955	960
30	Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln			
	965	970	975	
	Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro			
35	980	985	990	
	Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp			
40	995	1000	1005	
	Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe Phe			
	1010	1015	1020	
45	Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu Ser Ala			
	1025	1030	1035	1040
	Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn Gly Leu Gln			
50	1045	1050	1055	
	Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg Tyr Ser Ser Asp			
55	1060	1065	1070	

EP 1 439 393 A2

Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp Asp Thr Phe Leu Pro
5 1075 1080 1085
Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys Arg Pro Ala Gly Ser
1090 1095 1100
10 Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu Asn Pro Ala Pro Ser
1105 1110 1115 1120
Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr Ala Val Gly Asn Pro
15 1125 1130 1135
Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp
1140 1145 1150
20 Ser Pro Ala His Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp
1155 1160 1165
25 Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn
1170 1175 1180
Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val
30 1185 1190 1195 1200
Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala
1205 1210
35
40 <210> 126
<211> 1255
<212> PRT
45 <213> Homo sapiens
50 <400> 126
Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1 5 10 15
55 Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys

EP 1 439 393 A2

	20	25	30
5	Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His		
	35	40	45
	Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr		
10	50	55	60
	Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val		
	65	70	75
15	Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu		
	85	90	95
	Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr		
20	100	105	110
	Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro		
25	115	120	125
	Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser		
	130	135	140
30	Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln		
	145	150	155
	Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn		
35	165	170	175
	Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys		
40	180	185	190
	His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser		
	195	200	205
45	Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys		
	210	215	220
	Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys		
50	225	230	235
	Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu		
55	245	250	255

EP 1 439 393 A2

	His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala	Leu	Val
5																
	Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	Glu	Gly	Arg
10	Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	Tyr	Asn	Tyr	Leu
	Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	Pro	Leu	His	Asn	Gln
15																
	Glu	Val	Thr	Ala	Glu	Asp	Gly	Thr	Gln	Arg	Cys	Glu	Lys	Cys	Ser	Lys
20	Pro	Cys	Ala	Arg	Val	Cys	Tyr	Gly	Leu	Gly	Met	Glu	His	Leu	Arg	Glu
	Val	Arg	Ala	Val	Thr	Ser	Ala	Asn	Ile	Gln	Glu	Phe	Ala	Gly	Cys	Lys
25																
	Lys	Ile	Phe	Gly	Ser	Leu	Ala	Phe	Leu	Pro	Glu	Ser	Phe	Asp	Gly	Asp
30																
	Pro	Ala	Ser	Asn	Thr	Ala	Pro	Leu	Gln	Pro	Glu	Gln	Leu	Gln	Val	Phe
35	Glu	Thr	Leu	Glu	Glu	Ile	Thr	Gly	Tyr	Leu	Tyr	Ile	Ser	Ala	Trp	Pro
	Asp	Ser	Leu	Pro	Asp	Leu	Ser	Val	Phe	Gln	Asn	Leu	Gln	Val	Ile	Arg
40																
	Gly	Arg	Ile	Leu	His	Asn	Gly	Ala	Tyr	Ser	Leu	Thr	Leu	Gln	Gly	Leu
45																
	Gly	Ile	Ser	Trp	Leu	Gly	Leu	Arg	Ser	Leu	Arg	Glu	Leu	Gly	Ser	Gly
50	Leu	Ala	Leu	Ile	His	His	Asn	Thr	His	Leu	Cys	Phe	Val	His	Thr	Val
55	Pro	Trp	Asp	Gln	Leu	Phe	Arg	Asn	Pro	His	Gln	Ala	Leu	Leu	His	Thr

EP 1 439 393 A2

	485	490	495
5	Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His		
	500	505	510
	Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys		
10	515	520	525
	Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys		
	530	535	540
15	Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys		
	545	550	555
	Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys		
20	565	570	575
	Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp		
25	580	585	590
	Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu		
	595	600	605
30	Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln		
	610	615	620
	Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys		
35	625	630	635
	Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Val Ser		
40	645	650	655
	Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly		
	660	665	670
45	Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg		
	675	680	685
	Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly		
50	690	695	700
	Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu		
55	705	710	715
			720

EP 1 439 393 A2

	Arg	Lys	Val	Lys	Val	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Thr	Val	Tyr	Lys	
5					725					730						735	
	Gly	Ile	Trp	Ile	Pro	Asp	Gly	Glu	Asn	Val	Lys	Ile	Pro	Val	Ala	Ile	
					740					745						750	
10	Lys	Val	Leu	Arg	Glu	Asn	Thr	Ser	Pro	Lys	Ala	Asn	Lys	Glu	Ile	Leu	
					755					760						765	
	Asp	Glu	Ala	Tyr	Val	Met	Ala	Gly	Val	Gly	Ser	Pro	Tyr	Val	Ser	Arg	
15					770					775						780	
	Leu	Leu	Gly	Ile	Cys	Leu	Thr	Ser	Thr	Val	Gln	Leu	Val	Thr	Gln	Leu	
					785					790						795	
20	Met	Pro	Tyr	Gly	Cys	Leu	Leu	Asp	His	Val	Arg	Glu	Asn	Arg	Gly	Arg	
					805					810						815	
25	Leu	Gly	Ser	Gln	Asp	Leu	Leu	Asn	Trp	Cys	Met	Gln	Ile	Ala	Lys	Gly	
					820					825						830	
	Met	Ser	Tyr	Leu	Glu	Asp	Val	Arg	Leu	Val	His	Arg	Asp	Leu	Ala	Ala	
30					835					840						845	
	Arg	Asn	Val	Leu	Val	Lys	Ser	Pro	Asn	His	Val	Lys	Ile	Thr	Asp	Phe	
					850					855						860	
35	Gly	Leu	Ala	Arg	Leu	Leu	Asp	Ile	Asp	Glu	Thr	Glu	Tyr	His	Ala	Asp	
					865					870						875	
40	Gly	Gly	Lys	Val	Pro	Ile	Lys	Trp	Met	Ala	Leu	Glu	Ser	Ile	Leu	Arg	
					885					890						895	
	Arg	Arg	Phe	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Val	Thr	Val	
45					900					905						910	
	Trp	Glu	Leu	Met	Thr	Phe	Gly	Ala	Lys	Pro	Tyr	Asp	Gly	Ile	Pro	Ala	
					915					920						925	
50	Arg	Glu	Ile	Pro	Asp	Leu	Leu	Glu	Lys	Gly	Glu	Arg	Leu	Pro	Gln	Pro	
					930					935						940	
55	Pro	Ile	Cys	Thr	Ile	Asp	Val	Tyr	Met	Ile	Met	Val	Lys	Cys	Trp	Met	

EP 1 439 393 A2

	945	950	955	960
5	Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe			
		965	970	975
	Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu			
10		980	985	990
	Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu			
		995	1000	1005
15	Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu			
		1010	1015	1020
	Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly			
20		1025	1030	1035
	Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly			
		1045	1050	1055
25	Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg			
		1060	1065	1070
30	Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly			
		1075	1080	1085
	Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His			
35		1090	1095	1100
	Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu			
40		1105	1110	1115
	Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln			
		1125	1130	1135
45	Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro			
		1140	1145	1150
	Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu			
50		1155	1160	1165
	Arg Ala Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val			
55		1170	1175	1180

EP 1 439 393 A2

Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln
 1185 1190 1195 1200
 Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala
 1205 1210 1215
 Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala
 1220 1225 1230
 Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr
 1235 1240 1245
 Leu Gly Leu Asp Val Pro Val
 1250 1255
 <210> 127
 <211> 190
 <212> PRT
 <213> Homo sapiens
 <400> 127
 Met Thr Thr Ala Ser Thr Ser Gln Val Arg Gln Asn Tyr His Gln Asp
 1 5 10 15
 Ser Glu Ala Ala Ile Asn Arg Gln Ile Asn Leu Glu Leu Tyr Ala Ser
 20 25 30
 Tyr Val Tyr Leu Ser Met Ser Tyr Tyr Phe Asp Arg Asp Asp Val Ala
 35 40 45
 Leu Lys Asn Phe Ala Lys Tyr Phe Leu His Gln Ser His Glu Glu Arg
 50 55 60
 Glu His Ala Glu Lys Leu Met Lys Leu Gln Asn Gln Arg Gly Gly Arg
 65 70 75 80
 Ile Phe Leu Gln Asp Ile Lys Lys Pro Asp Cys Asp Asp Trp Glu Ser

EP 1 439 393 A2

	85	90	95
5	Gly Leu Asn Ala Met Glu Cys Ala Leu His Leu Glu Lys Asn Val Asn		
	100	105	110
	Gln Ser Leu Leu Glu Leu His Lys Leu Ala Thr Asp Lys Asn Asp Pro		
10	115	120	125
	His Leu Cys Asp Phe Ile Glu Thr His Tyr Leu Asn Glu Gln Val Lys		
	130	135	140
15	Ala Ile Lys Glu Leu Gly Asp His Val Thr Asn Leu Arg Lys Met Gly		
	145	150	155
	Ala Pro Glu Ser Gly Leu Ala Glu Tyr Leu Phe Asp Lys His Thr Trp		
20	165	170	175
	Glu Thr Val Ile Met Lys Ala Lys Pro Arg Ala Asn Phe Pro		
25	180	185	190
30	<210> 128		
	<211> 175		
	<212> PRT		
35	<213> Homo sapiens		
40	<400> 128		
	Met Ser Ser Gln Ile Arg Gln Asn Tyr Ser Thr Asp Val Glu Ala Ala		
	1	5	10
45	Val Asn Ser Leu Val Asn Leu Tyr Leu Gln Ala Ser Tyr Thr Tyr Leu		
	20	25	30
	Ser Leu Gly Phe Tyr Phe Asp Arg Asp Asp Val Ala Leu Glu Gly Val		
50	35	40	45
	Ser His Phe Phe Arg Glu Leu Ala Glu Glu Lys Arg Glu Gly Tyr Glu		
55	50	55	60

EP 1 439 393 A2

Arg Leu Leu Lys Met Gln Asn Gln Arg Gly Gly Arg Ala Leu Phe Gln
 5 65 70 75 80
 Asp Ile Lys Lys Pro Ala Glu Asp Glu Trp Gly Lys Thr Pro Asp Ala
 85 90 95
 10 Met Lys Ala Ala Met Ala Leu Glu Lys Lys Leu Asn Gln Ala Leu Leu
 100 105 110
 Asp Leu His Ala Leu Gly Ser Ala Arg Thr Asp Pro His Leu Cys Asp
 15 115 120 125
 Phe Leu Glu Thr His Phe Leu Asp Glu Glu Val Lys Leu Ile Lys Lys
 130 135 140
 20 Met Gly Asp His Leu Thr Asn Leu His Arg Leu Gly Gly Pro Glu Ala
 145 150 155 160
 25 Gly Leu Gly Glu Tyr Leu Phe Glu Arg Leu Thr Leu Lys His Asp
 165 170 175
 30
 <210> 129
 <211> 535
 35 <212> PRT
 <213> Homo sapiens
 40
 <400> 129
 Met Leu Gly Pro Cys Met Leu Leu Leu Leu Leu Leu Gly Leu Arg
 45 1 5 10 15
 Leu Gln Leu Ser Leu Gly Ile Ile Leu Val Glu Glu Glu Asn Pro Asp
 20 25 30
 50 Phe Trp Asn Arg Glu Ala Ala Glu Ala Leu Gly Ala Ala Lys Lys Leu
 35 40 45
 55 Gln Pro Ala Gln Thr Ala Ala Lys Asn Leu Ile Ile Phe Leu Gly Asp

EP 1 439 393 A2

	50	55	60	
5	Gly Met Gly Val Ser Thr Val Thr Ala Ala Arg Ile Leu Lys Gly Gln			
	65	70	75	80
	Lys Lys Asp Lys Leu Gly Pro Glu Ile Pro Leu Ala Met Asp Arg Phe			
10		85	90	95
	Pro Tyr Val Ala Leu Ser Lys Thr Tyr Asn Val Asp Lys His Val Pro			
	100	105	110	
15	Asp Ser Gly Ala Thr Ala Thr Ala Tyr Leu Cys Gly Val Lys Gly Asn			
	115	120	125	
20	Phe Gln Thr Ile Gly Leu Ser Ala Ala Ala Arg Phe Asn Gln Cys Asn			
	130	135	140	
	Thr Thr Arg Gly Asn Glu Val Ile Ser Val Met Asn Arg Ala Lys Lys			
25	145	150	155	160
	Ala Gly Lys Ser Val Gly Val Val Thr Thr Thr Arg Val Gln His Ala			
	165	170	175	
30	Ser Pro Ala Gly Thr Tyr Ala His Thr Val Asn Arg Asn Trp Tyr Ser			
	180	185	190	
35	Asp Ala Asp Val Pro Ala Ser Ala Arg Gln Glu Gly Cys Gln Asp Ile			
	195	200	205	
	Ala Thr Gln Leu Ile Ser Asn Met Asp Ile Asp Val Ile Leu Gly Gly			
40	210	215	220	
	Gly Arg Lys Tyr Met Phe Arg Met Gly Thr Pro Asp Pro Glu Tyr Pro			
	225	230	235	240
45	Asp Asp Tyr Ser Gln Gly Gly Thr Arg Leu Asp Gly Lys Asn Leu Val			
	245	250	255	
50	Gln Glu Trp Leu Ala Lys Arg Gln Gly Ala Arg Tyr Val Trp Asn Arg			
	260	265	270	
	Thr Glu Leu Met Gln Ala Ser Leu Asp Pro Ser Val Ala His Leu Met			
55	275	280	285	

EP 1 439 393 A2

Gly Leu Phe Glu Pro Gly Asp Met Lys Tyr Glu Ile His Arg Asp Ser
 5 290 295 300
 Thr Leu Asp Pro Ser Leu Met Glu Met Thr Glu Ala Ala Leu Arg Leu
 305 310 315 320
 10 Leu Ser Arg Asn Pro Arg Gly Phe Phe Leu Phe Val Glu Gly Gly Arg
 325 330 335
 Ile Asp His Gly His His Glu Ser Arg Ala Tyr Arg Ala Leu Thr Glu
 15 340 345 350
 Thr Ile Met Phe Asp Asp Ala Ile Glu Arg Ala Gly Gln Leu Thr Ser
 20 355 360 365
 Glu Glu Asp Thr Leu Ser Leu Val Thr Ala Asp His Ser His Val Phe
 370 375 380
 25 Ser Phe Gly Gly Tyr Pro Leu Arg Gly Ser Ser Ile Phe Gly Leu Ala
 385 390 395 400
 Pro Gly Lys Ala Arg Asp Arg Lys Ala Tyr Thr Val Leu Leu Tyr Gly
 30 405 410 415
 Asn Gly Pro Gly Tyr Val Leu Lys Asp Gly Ala Arg Pro Asp Val Thr
 420 425 430
 35 Glu Ser Glu Ser Gly Ser Pro Glu Tyr Arg Gln Gln Ser Ala Val Pro
 435 440 445
 40 Leu Asp Glu Glu Thr His Ala Gly Glu Asp Val Ala Val Phe Ala Arg
 450 455 460
 Gly Pro Gln Ala His Leu Val His Gly Val Gln Glu Gln Thr Phe Ile
 45 465 470 475 480
 Ala His Val Met Ala Phe Ala Ala Cys Leu Glu Pro Tyr Thr Ala Cys
 485 490 495
 50 Asp Leu Ala Pro Pro Ala Gly Thr Thr Asp Ala Ala His Pro Gly Arg
 500 505 510
 55 Ser Val Val Pro Ala Leu Leu Pro Leu Leu Ala Gly Thr Leu Leu Leu

EP 1 439 393 A2

515 520 525

5 Leu Glu Thr Ala Thr Ala Pro

530 535

10

<210> 130

<211> 461

15 <212> PRT

<213> Homo sapiens

20

<400> 130

Met Asn Asn Phe Gly Asn Glu Glu Phe Asp Cys His Phe Leu Asp Glu

25 1 5 10 15

Gly Phe Thr Ala Lys Asp Ile Leu Asp Gln Lys Ile Asn Glu Val Ser

20 25 30

30 Ser Ser Asp Asp Lys Asp Ala Phe Tyr Val Ala Asp Leu Gly Asp Ile

35 35 40 45

Leu Lys Lys His Leu Arg Trp Leu Lys Ala Leu Pro Arg Val Thr Pro

50 55 60

Phe Tyr Ala Val Lys Cys Asn Asp Ser Lys Ala Ile Val Lys Thr Leu

40 65 70 75 80

Ala Ala Thr Gly Thr Gly Phe Asp Cys Ala Ser Lys Thr Glu Ile Gln

85 90 95

45 Leu Val Gln Ser Leu Gly Val Pro Pro Glu Arg Ile Ile Tyr Ala Asn

100 105 110

50 Pro Cys Lys Gln Val Ser Gln Ile Lys Tyr Ala Ala Asn Asn Gly Val

115 120 125

Gln Met Met Thr Phe Asp Ser Glu Val Glu Leu Met Lys Val Ala Arg

55 130 135 140

EP 1 439 393 A2

Ala His Pro Lys Ala Lys Leu Val Leu Arg Ile Ala Thr Asp Asp Ser
5 145 150 155 160
Lys Ala Val Cys Arg Leu Ser Val Lys Phe Gly Ala Thr Leu Arg Thr
165 170 175
10 Ser Arg Leu Leu Leu Glu Arg Ala Lys Glu Leu Asn Ile Asp Val Val
180 185 190
Gly Val Ser Phe His Val Gly Ser Gly Cys Thr Asp Pro Glu Thr Phe
15 195 200 205
Val Gln Ala Ile Ser Asp Ala Arg Cys Val Phe Asp Met Gly Ala Glu
20 210 215 220
Val Gly Phe Ser Met Tyr Leu Leu Asp Ile Gly Gly Gly Phe Pro Gly
225 230 235 240
25 Ser Glu Asp Val Lys Leu Lys Phe Glu Glu Ile Thr Gly Val Ile Asn
245 250 255
Pro Ala Leu Asp Lys Tyr Phe Pro Ser Asp Ser Gly Val Arg Ile Ile
30 260 265 270
Ala Glu Pro Gly Arg Tyr Tyr Val Ala Ser Ala Phe Thr Leu Ala Val
35 275 280 285
Asn Ile Ile Ala Lys Lys Ile Val Leu Lys Glu Gln Thr Gly Ser Asp
290 295 300
40 Asp Glu Asp Glu Ser Ser Glu Gln Thr Phe Met Tyr Tyr Val Asn Asp
305 310 315 320
Gly Val Tyr Gly Ser Phe Asn Cys Ile Leu Tyr Asp His Ala His Val
45 325 330 335
Lys Pro Leu Leu Gln Lys Arg Pro Lys Pro Asp Glu Lys Tyr Tyr Ser
340 345 350
50 Ser Ser Ile Trp Gly Pro Thr Cys Asp Gly Leu Asp Arg Ile Val Glu
355 360 365
55 Arg Cys Asp Leu Pro Glu Met His Val Gly Asp Trp Met Leu Phe Glu

EP 1 439 393 A2

370 375 380
 5 Asn Met Gly Ala Tyr Thr Val Ala Ala Ala Ser Thr Phe Asn Gly Phe
 385 390 395 400
 Gln Arg Pro Thr Ile Tyr Tyr Val Met Ser Gly Pro Ala Trp Gln Leu
 10 405 410 415
 Met Gln Gln Phe Gln Asn Pro Asp Phe Pro Pro Glu Val Glu Glu Gln
 420 425 430
 15 Asp Ala Ser Thr Leu Pro Val Ser Cys Ala Trp Glu Ser Gly Met Lys
 435 440 445
 20 Arg His Arg Ala Ala Cys Ala Ser Ala Ser Ile Asn Val
 450 455 460
 25
 <210> 131
 <211> 1148
 30 <212> PRT
 <213> Homo sapiens
 35
 <400> 131
 Met Pro Leu Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys
 40 1 5 10 15
 Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val
 20 25 30
 45 Asp Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp
 35 40 45
 Arg Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr
 50 50 55 60
 Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly
 55 65 70 75 80

EP 1 439 393 A2

	Phe	Thr	His	Gln	Ser	Ser	Met	Thr	Thr	Thr	Arg	Thr	Pro	Asp	Thr	Ser
5					85					90					95	
	Thr	Met	His	Leu	Ala	Thr	Ser	Arg	Thr	Pro	Ala	Ser	Leu	Ser	Gly	Pro
					100					105					110	
10	Thr	Thr	Ala	Ser	Pro	Leu	Leu	Val	Leu	Phe	Thr	Ile	Asn	Phe	Thr	Ile
					115					120					125	
	Thr	Asn	Leu	Arg	Tyr	Glu	Glu	Asn	Met	His	His	Pro	Gly	Ser	Arg	Lys
15					130					135					140	
	Phe	Asn	Thr	Thr	Glu	Arg	Val	Leu	Gln	Gly	Leu	Leu	Arg	Pro	Val	Phe
20					145					150				155		160
	Lys	Asn	Thr	Ser	Val	Gly	Pro	Leu	Tyr	Ser	Gly	Cys	Arg	Leu	Thr	Leu
					165					170					175	
25	Leu	Arg	Pro	Lys	Lys	Asp	Gly	Ala	Ala	Thr	Lys	Val	Asp	Ala	Ile	Cys
					180					185					190	
	Thr	Tyr	Arg	Pro	Asp	Pro	Lys	Ser	Pro	Gly	Leu	Asp	Arg	Glu	Gln	Leu
30					195					200					205	
	Tyr	Trp	Glu	Leu	Ser	Gln	Leu	Thr	His	Ser	Ile	Thr	Glu	Leu	Gly	Pro
35					210					215					220	
	Tyr	Thr	Leu	Asp	Arg	Asp	Ser	Leu	Tyr	Val	Asn	Gly	Phe	Thr	Gln	Arg
					225					230				235		240
40	Ser	Ser	Val	Pro	Thr	Thr	Ser	Ile	Pro	Gly	Thr	Pro	Thr	Val	Asp	Leu
					245					250					255	
	Gly	Thr	Ser	Gly	Thr	Pro	Val	Ser	Lys	Pro	Gly	Pro	Ser	Ala	Ala	Ser
45					260					265					270	
	Pro	Leu	Leu	Val	Leu	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Arg
50					275					280					285	
	Tyr	Glu	Glu	Asn	Met	Gln	His	Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr
					290					295					300	
55	Glu	Arg	Val	Leu	Gln	Gly	Leu	Leu	Arg	Ser	Leu	Phe	Lys	Ser	Thr	Ser

EP 1 439 393 A2

	305	310	315	320
5	Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu			
		325	330	335
	Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro			
10		340	345	350
	Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu			
		355	360	365
15	Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly His Tyr Ala Leu Asp			
		370	375	380
20	Asn Asp Ser Leu Phe Val Asn Gly Phe Thr His Arg Ser Ser Val Ser			
		385	390	395
	Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys			
25		405	410	415
	Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile			
		420	425	430
30	Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn			
		435	440	445
35	Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln			
		450	455	460
	Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr			
40		465	470	475
	Ser Gly Ser Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala			
		485	490	495
45	Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro			
		500	505	510
	Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His			
50		515	520	525
	Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr			
55		530	535	540

EP 1 439 393 A2

Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly
5 545 550 555 560
Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu
565 570 575
10 Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile
580 585 590
Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser
15 595 600 605
Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser
20 610 615 620
Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu
625 630 635 640
25 Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu
645 650 655
Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu
30 660 665 670
Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Leu Asp
675 680 685
35 Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu
690 695 700
40 Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu
705 710 715 720
Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly
45 725 730 735
Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg
740 745 750
50 Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln
755 760 765
55 Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp

EP 1 439 393 A2

	770	775	780	
5	Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile			
	785	790	795	800
	Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln			
10		805	810	815
	Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr			
		820	825	830
15	Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His			
		835	840	845
	Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr			
20		850	855	860
	Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys			
25	865	870	875	880
	Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu			
		885	890	895
30	Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn			
		900	905	910
	Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn			
35		915	920	925
	Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His			
40		930	935	940
	Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser			
	945	950	955	960
45	Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser			
		965	970	975
	Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg			
50		980	985	990
	Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys			
55		995	1000	1005

EP 1 439 393 A2

Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn
 5 1010 1015 1020
 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala
 1025 1030 1035 1040
 10 Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr
 1045 1050 1055
 Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val
 15 1060 1065 1070
 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn
 20 1075 1080 1085
 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu
 1090 1095 1100
 25 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg
 1105 1110 1115 1120
 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly
 30 1125 1130 1135
 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
 35 1140 1145

 40 <210> 132
 <211> 526
 <212> PRT
 45 <213> Homo sapiens

 50 <400> 132
 Met Gly His Leu Ser Ala Pro Leu His Arg Val Arg Val Pro Trp Gln
 1 5 10 15
 55 Gly Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr

EP 1 439 393 A2

	20	25	30
5	Thr Ala Gln Leu Thr Thr Glu Ser Met Pro Phe Asn Val Ala Glu Gly		
	35	40	45
	Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln Gln Leu Phe Gly		
10	50	55	60
	Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Val		
	65	70	75
15	Gly Tyr Ala Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Asn Ser		
	85	90	95
20	Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val		
	100	105	110
	Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp		
25	115	120	125
	Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu		
	130	135	140
30	Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys		
	145	150	155
	Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Thr Thr Tyr		
35	165	170	175
	Leu Trp Trp Ile Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln		
40	180	185	190
	Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Leu Ser Val Thr Arg Asn		
	195	200	205
45	Asp Thr Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Val Ser Ala Asn		
	210	215	220
	Arg Ser Asp Pro Val Thr Leu Asn Val Thr Tyr Gly Pro Asp Thr Pro		
50	225	230	235
	Thr Ile Ser Pro Ser Asp Thr Tyr Tyr Arg Pro Gly Ala Asn Leu Ser		
55	245	250	255

EP 1 439 393 A2

Leu Ser Cys Tyr Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Leu
 5 260 265 270
 Ile Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn
 275 280 285
 10 Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys His Ala Asn Asn Ser
 290 295 300
 Val Thr Gly Cys Asn Arg Thr Thr Val Lys Thr Ile Ile Val Thr Glu
 15 305 310 315 320
 Leu Ser Pro Val Val Ala Lys Pro Gln Ile Lys Ala Ser Lys Thr Thr
 20 325 330 335
 Val Thr Gly Asp Lys Asp Ser Val Asn Leu Thr Cys Ser Thr Asn Asp
 340 345 350
 25 Thr Gly Ile Ser Ile Arg Trp Phe Phe Lys Asn Gln Ser Leu Pro Ser
 355 360 365
 Ser Glu Arg Met Lys Leu Ser Gln Gly Asn Thr Thr Leu Ser Ile Asn
 30 370 375 380
 Pro Val Lys Arg Glu Asp Ala Gly Thr Tyr Trp Cys Glu Val Phe Asn
 35 385 390 395 400
 Pro Ile Ser Lys Asn Gln Ser Asp Pro Ile Met Leu Asn Val Asn Tyr
 405 410 415
 40 Asn Ala Leu Pro Gln Glu Asn Gly Leu Ser Pro Gly Ala Ile Ala Gly
 420 425 430
 Ile Val Ile Gly Val Val Ala Leu Val Ala Leu Ile Ala Val Ala Leu
 45 435 440 445
 Ala Cys Phe Leu His Phe Gly Lys Thr Gly Arg Ala Ser Asp Gln Arg
 450 455 460
 50 Asp Leu Thr Glu His Lys Pro Ser Val Ser Asn His Thr Gln Asp His
 465 470 475 480
 55 Ser Asn Asp Pro Pro Asn Lys Met Asn Glu Val Thr Tyr Ser Thr Leu

EP 1 439 393 A2

	485	490	495
5	Asn Phe Glu Ala Gln Gln Pro Thr Gln Pro Thr Ser Ala Ser Pro Ser		
	500	505	510
	Leu Thr Ala Thr Glu Ile Ile Tyr Ser Glu Val Lys Lys Gln		
10	515	520	525
15	<210> 133		
	<211> 212		
20	<212> PRT		
	<213> Homo sapiens		
25	<400> 133		
	Met Gly Pro Pro Ser Ala Pro Pro His Arg Glu Cys Ile Pro Trp Gln		
	1 5 10 15		
30	Gly Leu Leu Leu Thr Ala Ser Leu Leu Asn Phe Trp Asn Pro Pro Thr		
	20 25 30		
35	Thr Ala Lys Leu Thr Ile Glu Ser Met Pro Leu Ser Val Ala Glu Gly		
	35 40 45		
	Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly		
40	50 55 60		
	Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val		
	65 70 75 80		
45	Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Ala Ala Tyr Ser		
	85 90 95		
	Gly Arg Glu Thr Ile Tyr Thr Asn Ala Ser Leu Leu Ile Gln Asn Val		
50	100 105 110		
	Thr Gln Asn Asp Ile Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp		
55	115 120 125		

EP 1 439 393 A2

Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Gln Glu Asn
 5 130 135 140
 Ala Pro Gly Leu Pro Val Gly Ala Val Ala Gly Ile Val Thr Gly Val
 145 150 155 160
 10 Leu Val Gly Val Ala Leu Val Ala Ala Leu Val Cys Phe Leu Leu Leu
 165 170 175
 Ala Lys Thr Gly Arg Pro Trp Ser Leu Pro Gln Leu Cys Leu Leu Asp
 15 180 185 190
 Val Pro Ser Leu His Cys Leu Gly Pro Pro Thr Gln Pro Gln Asp Ser
 20 195 200 205
 Ser Phe His Leu
 210
 25
 <210> 134
 30 <211> 244
 <212> PRT
 35 <213> Homo sapiens

 <400> 134
 40 Met Gly Pro Pro Ser Ala Ala Pro Arg Gly Gly His Arg Pro Trp Gln
 1 5 10 15
 Gly Leu Leu Ile Thr Ala Ser Leu Leu Thr Phe Trp Asp Pro Pro Thr
 45 20 25 30
 Thr Val Gln Phe Thr Ile Glu Ala Leu Pro Ser Ser Ala Ala Glu Gly
 35 40 45
 50 Lys Asp Val Leu Leu Leu Ala Cys Asn Ile Ser Glu Thr Ile Gln Ala
 50 55 60
 55 Tyr Tyr Trp His Lys Gly Lys Thr Ala Glu Gly Ser Pro Leu Ile Ala

EP 1 439 393 A2

65 70 75 80
5 Gly Tyr Ile Thr Asp Ile Gln Ala Asn Ile Pro Gly Ala Ala Tyr Ser
85 90 95
Gly Arg Glu Gln Val Tyr Pro Asn Gly Ser Leu Leu Phe Gln Asn Ile
10 100 105 110
Thr Leu Glu Asp Ala Gly Ser Tyr Thr Leu Arg Thr Ile Asn Ala Ser
115 120 125
15 Tyr Asp Ser Asp Gln Ala Thr Gly Gln Leu His Val His Gln Asn Asn
130 135 140
Val Pro Gly Leu Pro Val Gly Ala Val Ala Gly Ile Val Thr Gly Val
20 145 150 155 160
Leu Val Gly Val Ala Leu Val Ala Ala Leu Val Cys Phe Leu Leu Leu
25 165 170 175
Ser Arg Thr Gly Arg Ala Ser Ile Gln Arg Asp Leu Arg Glu Gln Pro
180 185 190
30 Pro Pro Ala Ser Thr Pro Gly His Gly Pro Ser His Arg Ser Thr Phe
195 200 205
Ser Ala Pro Leu Pro Ser Pro Arg Thr Ala Thr Pro Ile Tyr Val Glu
35 210 215 220
Phe Leu Tyr Ser Asp Ala Asn Ile Tyr Cys Gln Ile Asp His Lys Ala
40 225 230 235 240
Asp Val Val Ser

45

<210> 135

50

<211> 344

<212> PRT

55

<213> Homo sapiens

5 <400> 135
 Met Gly Pro Pro Ser Ala Pro Pro Cys Arg Leu His Val Pro Trp Lys
 1 5 10 15
 10 Glu Val Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
 20 25 30
 Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
 15 35 40 45
 Lys Glu Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly
 20 50 55 60
 Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val
 65 70 75 80
 25 Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser
 85 90 95
 Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val
 30 100 105 110
 Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp
 115 120 125
 35 Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu
 130 135 140
 40 Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys
 145 150 155 160
 Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr
 45 165 170 175
 Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
 180 185 190
 50 Leu Ser Asn Gly Asn Met Thr Leu Thr Leu Leu Ser Val Lys Arg Asn
 195 200 205
 55 Asp Ala Gly Ser Tyr Glu Cys Glu Ile Gln Asn Pro Ala Ser Ala Asn

EP 1 439 393 A2

	210	215	220	
5	Arg Ser Asp Pro Val Thr Leu Asn Val Leu Tyr Gly Pro Asp Val Pro			
	225	230	235	240
	Thr Ile Ser Pro Ser Lys Ala Asn Tyr Arg Pro Gly Glu Asn Leu Asn			
10		245	250	255
	Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe			
	260	265	270	
15	Ile Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn			
	275	280	285	
20	Ile Thr Val Asn Asn Ser Gly Ser Tyr Met Cys Gln Ala His Asn Ser			
	290	295	300	
	Ala Thr Gly Leu Asn Arg Thr Thr Val Thr Met Ile Thr Val Ser Gly			
25	305	310	315	320
	Ser Ala Pro Val Leu Ser Ala Val Ala Thr Val Gly Ile Thr Ile Gly			
	325	330	335	
30	Val Leu Ala Arg Val Ala Leu Ile			
	340			
35				
	<210> 136			
40	<211> 265			
	<212> PRT			
	<213> Homo sapiens			
45				
	<400> 136			
50	Met Gly Ser Pro Ser Ala Cys Pro Tyr Arg Val Cys Ile Pro Trp Gln			
	1	5	10	15
	Gly Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Leu Pro Asn			
55	20	25	30	

EP 1 439 393 A2

Ser Ala Gln Thr Asn Ile Asp Val Val Pro Phe Asn Val Ala Glu Gly
 5 35 40 45
 Lys Glu Val Leu Leu Val Val His Asn Glu Ser Gln Asn Leu Tyr Gly
 50 55 60
 10 Tyr Asn Trp Tyr Lys Gly Glu Arg Val His Ala Asn Tyr Arg Ile Ile
 65 70 75 80
 Gly Tyr Val Lys Asn Ile Ser Gln Glu Asn Ala Pro Gly Pro Ala His
 15 85 90 95
 Asn Gly Arg Glu Thr Ile Tyr Pro Asn Gly Thr Leu Leu Ile Gln Asn
 100 105 110
 20 Val Thr His Asn Asp Ala Gly Phe Tyr Thr Leu His Val Ile Lys Glu
 115 120 125
 25 Asn Leu Val Asn Glu Glu Val Thr Arg Gln Phe Tyr Val Phe Ser Glu
 130 135 140
 Pro Pro Lys Pro Ser Ile Thr Ser Asn Asn Phe Asn Pro Val Glu Asn
 30 145 150 155 160
 Lys Asp Ile Val Val Leu Thr Cys Gln Pro Glu Thr Gln Asn Thr Thr
 165 170 175
 35 Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Leu Val Ser Pro Arg Leu
 180 185 190
 40 Leu Leu Ser Thr Asp Asn Arg Thr Leu Val Leu Leu Ser Ala Thr Lys
 195 200 205
 Asn Asp Ile Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Val Gly Ala
 45 210 215 220
 Ser Arg Ser Asp Pro Val Thr Leu Asn Val Arg Tyr Glu Ser Val Gln
 225 230 235 240
 50 Ala Ser Ser Pro Asp Leu Ser Ala Gly Thr Ala Val Ser Ile Met Ile
 245 250 255
 55 Gly Val Leu Ala Gly Met Ala Leu Ile

EP 1 439 393 A2

260 265

5

<210> 137

10 <211> 349

<212> PRT

<213> Homo sapiens

15

<400> 137

20 Met Gly Pro Ile Ser Ala Pro Ser Cys Arg Trp Arg Ile Pro Trp Gln

1 5 10 15

Gly Leu Leu Leu Thr Ala Ser Leu Phe Thr Phe Trp Asn Pro Pro Thr

25 20 25 30

Thr Ala Gln Leu Thr Ile Glu Ala Val Pro Ser Asn Ala Ala Glu Gly

35 40 45

30 Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln Asp Pro Arg Gly

50 55 60

Tyr Asn Trp Tyr Lys Gly Glu Thr Val Asp Ala Asn Arg Arg Ile Ile

35 65 70 75 80

Gly Tyr Val Ile Ser Asn Gln Gln Ile Thr Pro Gly Pro Ala Tyr Ser

40 85 90 95

Asn Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Met Arg Asn Val

100 105 110

45 Thr Arg Asn Asp Thr Gly Ser Tyr Thr Leu Gln Val Ile Lys Leu Asn

115 120 125

Leu Met Ser Glu Glu Val Thr Gly Gln Phe Ser Val His Pro Glu Thr

50 130 135 140

Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys

55 145 150 155 160

EP 1 439 393 A2

Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asn Thr Thr Tyr
 165 170 175
 5 Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Arg Leu Gln
 180 185 190
 10 Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Leu Ser Val Thr Arg Asn
 195 200 205
 Asp Val Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Ala Ser Ala Asn
 15 210 215 220
 Phe Ser Asp Pro Val Thr Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro
 225 230 235 240
 20 Thr Ile Ser Pro Ser Asp Thr Tyr Tyr His Ala Gly Val Asn Leu Asn
 245 250 255
 25 Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ser Gln Tyr Ser Trp Ser
 260 265 270
 Val Asn Gly Thr Phe Gln Gln Tyr Thr Gln Lys Leu Phe Ile Pro Asn
 30 275 280 285
 Ile Thr Thr Lys Asn Ser Gly Ser Tyr Ala Cys His Thr Thr Asn Ser
 290 295 300
 35 Ala Thr Gly Arg Asn Arg Thr Thr Val Arg Met Ile Thr Val Ser Asp
 305 310 315 320
 40 Ala Leu Val Gln Gly Ser Ser Pro Gly Leu Ser Ala Arg Ala Thr Val
 325 330 335
 Ser Ile Met Ile Gly Val Leu Ala Arg Val Ala Leu Ile
 45 340 345
 50 <210> 138
 <211> 459
 55 <212> PRT

EP 1 439 393 A2

<213> Homo sapiens

5

<400> 138

	Met	Ala	Pro	Leu	Cys	Pro	Ser	Pro	Trp	Leu	Pro	Leu	Leu	Ile	Pro	Ala
10	1				5					10					15	
	Pro	Ala	Pro	Gly	Leu	Thr	Val	Gln	Leu	Leu	Leu	Ser	Leu	Leu	Leu	Leu
				20				25					30			
15	Met	Pro	Val	His	Pro	Gln	Arg	Leu	Pro	Arg	Met	Gln	Glu	Asp	Ser	Pro
			35				40					45				
	Leu	Gly	Gly	Gly	Ser	Ser	Gly	Glu	Asp	Asp	Pro	Leu	Gly	Glu	Glu	Asp
20			50				55					60				
	Leu	Pro	Ser	Glu	Glu	Asp	Ser	Pro	Arg	Glu	Glu	Asp	Pro	Pro	Gly	Glu
25	65				70					75					80	
	Glu	Asp	Leu	Pro	Gly	Glu	Glu	Asp	Leu	Pro	Gly	Glu	Glu	Asp	Leu	Pro
				85					90					95		
30	Glu	Val	Lys	Pro	Lys	Ser	Glu	Glu	Glu	Gly	Ser	Leu	Lys	Leu	Glu	Asp
			100						105					110		
	Leu	Pro	Thr	Val	Glu	Ala	Pro	Gly	Asp	Pro	Gln	Glu	Pro	Gln	Asn	Asn
35			115						120					125		
	Ala	His	Arg	Asp	Lys	Glu	Gly	Asp	Asp	Gln	Ser	His	Trp	Arg	Tyr	Gly
40		130					135						140			
	Gly	Asp	Pro	Pro	Trp	Pro	Arg	Val	Ser	Pro	Ala	Cys	Ala	Gly	Arg	Phe
	145				150					155				160		
45	Gln	Ser	Pro	Val	Asp	Ile	Arg	Pro	Gln	Leu	Ala	Ala	Phe	Cys	Pro	Ala
				165					170					175		
	Leu	Arg	Pro	Leu	Glu	Leu	Leu	Gly	Phe	Gln	Leu	Pro	Pro	Leu	Pro	Glu
50			180						185					190		
	Leu	Arg	Leu	Arg	Asn	Asn	Gly	His	Ser	Val	Gln	Leu	Thr	Leu	Pro	Pro
55			195						200					205		

EP 1 439 393 A2

Gly Leu Glu Met Ala Leu Gly Pro Gly Arg Glu Tyr Arg Ala Leu Gln
 5 210 215 220
 Leu His Leu His Trp Gly Ala Ala Gly Arg Pro Gly Ser Glu His Thr
 225 230 235 240
 10 Val Glu Gly His Arg Phe Pro Ala Glu Ile His Val Val His Leu Ser
 245 250 255
 Thr Ala Phe Ala Arg Val Asp Glu Ala Leu Gly Arg Pro Gly Gly Leu
 15 260 265 270
 Ala Val Leu Ala Ala Phe Leu Glu Glu Gly Pro Glu Glu Asn Ser Ala
 20 275 280 285
 Tyr Glu Gln Leu Leu Ser Arg Leu Glu Glu Ile Ala Glu Glu Gly Ser
 290 295 300
 25 Glu Thr Gln Val Pro Gly Leu Asp Ile Ser Ala Leu Leu Pro Ser Asp
 305 310 315 320
 Phe Ser Arg Tyr Phe Gln Tyr Glu Gly Ser Leu Thr Thr Pro Pro Cys
 30 325 330 335
 Ala Gln Gly Val Ile Trp Thr Val Phe Asn Gln Thr Val Met Leu Ser
 340 345 350
 35 Ala Lys Gln Leu His Thr Leu Ser Asp Thr Leu Trp Gly Pro Gly Asp
 355 360 365
 40 Ser Arg Leu Gln Leu Asn Phe Arg Ala Thr Gln Pro Leu Asn Gly Arg
 370 375 380
 Val Ile Glu Ala Ser Phe Pro Ala Gly Val Asp Ser Ser Pro Arg Ala
 45 385 390 395 400
 Ala Glu Pro Val Gln Leu Asn Ser Cys Leu Ala Ala Gly Asp Ile Leu
 405 410 415
 50 Ala Leu Val Phe Gly Leu Leu Phe Ala Val Thr Ser Val Ala Phe Leu
 420 425 430
 55 Val Gln Met Arg Arg Gln His Arg Arg Gly Thr Lys Gly Gly Val Ser

435

440

445

5 Tyr Arg Pro Ala Glu Val Ala Glu Thr Gly Ala

450

455

10

15 Claims

1. A method of diagnosing colon cancer in an individual comprising:

(a) obtaining a serum sample from said individual; and

(b) detecting the presence of TIMP 1 in said sample, wherein the presence of TIMP 1 in said sample is indicative of colon cancer in said individual.

2. The method of claim 1, wherein said step of detecting comprises:

(a) contacting said serum sample with a polypeptide ligand which is capable of binding to TIMP1 under conditions which permit said polypeptide ligand to bind to TIMP1; and

(b) detecting the binding of said polypeptide ligand to TIMP1, wherein detection of binding is indicative of the presence of TIMP1 in said sample.

3. The method of claim 2, wherein said polypeptide ligand is an antibody.

4. The method of claim 2 or claim 3, wherein said polypeptide ligand comprises a detectable label.

5. The method of any one of the preceding claims, wherein said individual is a human.

6. The method of any one of the preceding claims, further comprising detecting at least one other colon cancer specific marker in said sample, wherein the presence of TIMP 1 and said at least one other colon cancer-specific marker is indicative of colon cancer in said individual.

7. The method of claim 6, wherein said colon cancer-specific marker is selected from the group consisting of the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, the polypeptide molecules of SEQ ID Nos 2, 4, 72-138, CA 19-9, CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and Du-PAN 1 - 5.

8. The method of claim 6 or claim 7, wherein said step of detecting comprises:

(a) contacting said serum sample with a first polypeptide ligand which is capable of binding to TIMP1 and a second polypeptide ligand which is capable of binding to said colon cancer-specific marker, under conditions which permit said first and second polypeptide ligands to bind to TIMP 1 and said colon cancer-specific marker, respectively; and

(b) detecting the binding of said first polypeptide ligand to TIMP 1 and said second polypeptide ligand to said colon cancer-specific marker, wherein detection of binding is indicative of the presence of TIMP1 and said colon cancer-specific marker in said sample.

9. The method of claim 8, wherein said first and second polypeptide ligand are each an antibody.

10. The method of claim 8 or claim 9, wherein said first and second polypeptide ligand comprises a detectable label.

11. The method of any one of claims 1 to 10, further comprising the step of detecting the presence of REG1 α in said sample, wherein the presence of REG1 α in said sample is indicative of colon cancer in said individual.

12. A method of diagnosing colon cancer in an individual comprising:

(a) obtaining a serum sample from an individual; and

(b) detecting the presence of a nucleic acid molecule which encodes TIMP1 in said sample, wherein the presence of TIMP1 of said nucleic acid molecule in said sample is indicative of colon cancer in said individual.

13. The method of claim 12, further comprising detecting at least one other nucleic acid molecule which encodes at least one other colon cancer-specific marker in said sample, wherein the presence of said nucleic acid sequence encoding TIMP1 and said nucleic acid sequence encoding said at least one other colon cancer-specific marker is indicative of colon cancer in said individual.

14. The method of claim 12 or claim 13, wherein said colon cancer specific marker is selected from the group consisting of SEQ ID Nos 1, 3, 5-71, the polypeptide molecules of SEQ ID Nos 2, 4, 72-138, CA 19-9, CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and Du - PAN 1 - 5.

15. The method of any one of claims 12 to 14, further comprising the step of detecting presence of a nucleic acid molecule which encodes REG1 α in said sample, wherein the presence of REG1 α of said nucleic acid molecule in said sample is indicative of colon cancer in said individual.

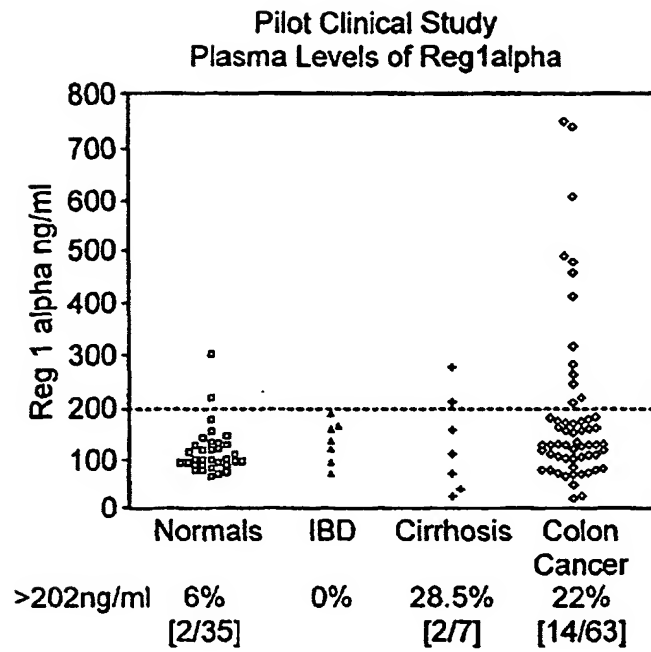


FIG. 1

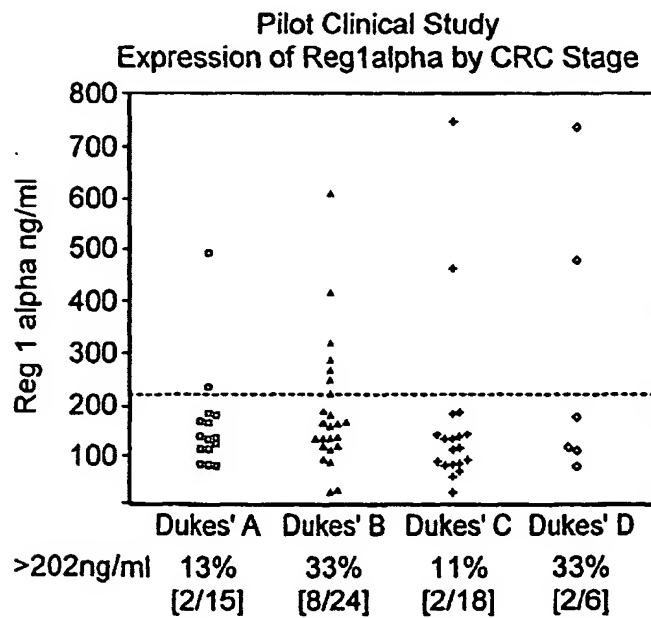


FIG. 2

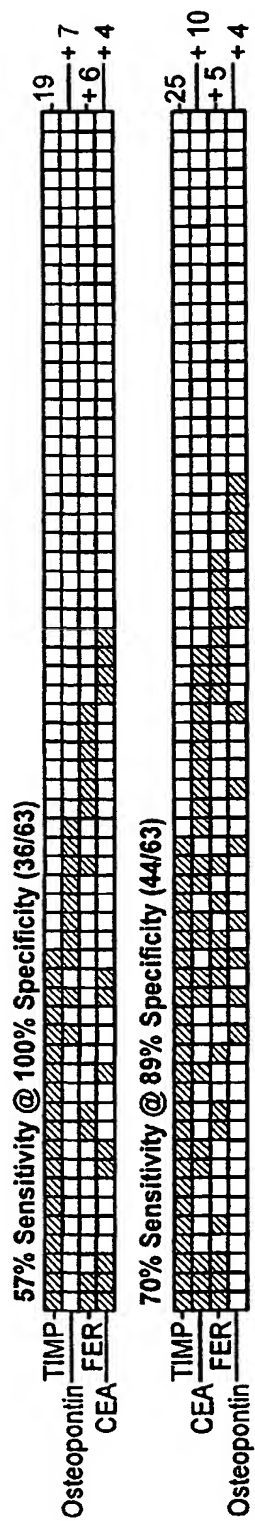
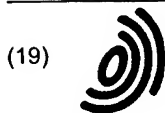


FIG. 3



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 1 439 393 A3**

(12) **EUROPEAN PATENT APPLICATION**

(88) Date of publication A3:
11.08.2004 Bulletin 2004/33

(51) Int Cl.7: **G01N 33/574, G01N 33/53**

(43) Date of publication A2:
21.07.2004 Bulletin 2004/30

(21) Application number: **03257868.4**

(22) Date of filing: **15.12.2003**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IT LI LU MC NL PT RO SE SI SK TR**
Designated Extension States:
AL LT LV MK

(30) Priority: **13.12.2002 US 433554 P**
31.07.2003 US 491397 P

(71) Applicants:
• **Bayer Healthcare LLC**
Tarrytown, New York 10591-5097 (US)
• **MAYO FOUNDATION FOR MEDICAL
EDUCATION AND RESEARCH**
Rochester, MN 55905 (US)

(72) Inventors:
• **Astle, Jon H.**
Taunton, MA 02780 (US)
• **Boardman, Lisa Allyn**
Rochester, MN 55902 (US)
• **Bugart, Lawrence J.**
Rochester, MN 55901 (US)
• **Burgess, Christopher C.**
Westwood, MA 02090 (US)
• **Catino, Theodore J.**
Attleboro, MA 02702 (US)

• **Dwivedi, Poornima**
Alamo, CA 94507 (US)
• **Huntress, Maryanne**
Attleboro, MA 02703 (US)
• **Johnson, Karen Anne**
Action, MA 01720 (US)
• **Lewis, Marcia E.**
Cohasset, MA 02025 (US)
• **Maimonis, Peter J.**
Westwood, MA 02090 (US)
• **Myerow, Susan H.**
Lexington, MA 02421 (US)
• **Brown-Shimer, Sheryl Lynn Andrea**
Boston, MA 02118 (US)
• **Thiagalingam, Arunthathi**
Lexington, MA 02420 (US)
• **Thibodeau, Stephen N.**
Rochester, MN 55906 (US)
• **Molino, Gary A.**
Norfolk, MA 02056 (US)

(74) Representative: **Grant, Anne Rosemary**
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4V 4EL (GB)

(54) **Detection methods using TIMP 1 for colon cancer diagnosis**

(57) The present invention relates to a method for detecting the presence of colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 α or TIMP1 nucleic acid or amino acid molecules in a clinical sample obtained from the patient, wherein Reg1 α or TIMP1 expression is indicative of the presence of colorectal cancer. The invention further relates to a method for detecting the presence of

colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 α or TIMP1 nucleic acid or amino acid molecules in a clinical sample, in addition to detecting the presence of one or more additional colorectal cancer associated markers.

EP 1 439 393 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 03 25 7868

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	XIAI QING LU ET AL: "IMMUNOLOGICAL QUANTIFICATION OF LEVELS OF TISSUE INHIBITOR OF METALLOPROTEINASE-1 IN HUMAN COLON CANCER" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 51, no. 23, PART 1, 1 December 1991 (1991-12-01), pages 6231-6235, XP000609477 ISSN: 0008-5472 * page 6232 - page 6234 *	1-15	G01N33/574 G01N33/53
X	WO 02/086085 A (KREBS BARBARA ;KNORR ANDREAS M (DE); KRAFT SABINE (DE); MORPHOSYS) 31 October 2002 (2002-10-31) * abstract; claims *	1-15	
X	WO 01/12781 A (HUMAN GENOME SCIENCES INC ;ROSEN CRAIG A (US); BIRSE CHARLES E (US) 22 February 2001 (2001-02-22) Sequence ID numbers 1 and 14 * abstract; claims *	1-15	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	HOLTON-ANDERSEN M N ET AL: "Measurement of the noncomplexed free fraction of tissue inhibitor of metalloproteinases 1 in plasma by immunoassay" CLINICAL CHEMISTRY, AMERICAN ASSOCIATION FOR CLINICAL CHEMISTRY, WINSTON, US, vol. 48, no. 8, August 2002 (2002-08), pages 1305-1313, XP002959679 ISSN: 0009-9147 * page 1305 - page 1306 *	1-15	G01N
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 26 May 2004	Examiner GONCALVES M L F C
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.02 (P04C01)



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 03 25 7868

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	HARADA K ET AL: "Human REG I gene is up-regulated in intrahepatic cholangiocarcinoma and its precursor lesions." HEPATOLOGY (BALTIMORE, MD.) UNITED STATES MAY 2001, vol. 33, no. 5, May 2001 (2001-05), pages 1036-1042, XP002282254 ISSN: 0270-9139 * page 1036 - page 1037 *	11,15	
X	PELLEGRINI P ET AL: "Simultaneous measurement of soluble carcinoembryonic antigen and the tissue inhibitor of metalloproteinase TIMP1 serum levels for use as markers of pre-invasive to invasive colorectal cancer." CANCER IMMUNOLOGY, IMMUNOTHERAPY: CII. GERMANY SEP 2000, vol. 49, no. 7, September 2000 (2000-09), pages 388-394, XP002282255 ISSN: 0340-7004 * page 388 - page 390 *	1-15	
X	OKUNO K ET AL: "Gene expression analysis in colorectal cancer using practical DNA array filter." DISEASES OF THE COLON AND RECTUM. UNITED STATES FEB 2001, vol. 44, no. 2, February 2001 (2001-02), pages 295-299, XP009031427 ISSN: 0012-3706 * page 298 - page 299; figures 2,3; table 2 *	1-15	
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 26 May 2004	Examiner GONCALVES M L F C
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 (03.02) (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 03 25 7868

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

26-05-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02086085 A	31-10-2002	CA 2445168 A1	31-10-2002
		EP 1381631 A2	21-01-2004
		WO 02086085 A2	31-10-2002
WO 0112781 A	22-02-2001	AU 7058000 A	13-03-2001
		CA 2385487 A1	22-02-2001
		EP 1208191 A1	29-05-2002
		JP 2003507033 T	25-02-2003
		WO 0112781 A1	22-02-2001
		US 2003203361 A1	30-10-2003

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☒ ~~FADED~~ TEXT OR DRAWING

☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☐ GRAY SCALE DOCUMENTS

☐ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.